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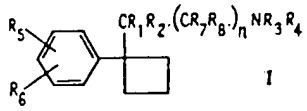
(54) Therapeutic agents

(57) Compounds of formula I



I

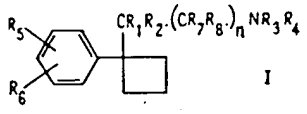
in which n=0 or 1; R_1 is C_{1-} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, cycloalkylalkyl or optionally substituted phenyl when n=0 or R_1 is H or C_{1-3} alkyl when n=1, R_2 is H or C_{1-3} alkyl, R_3 and/or R_4 are H, formyl, C_{1-3} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{3-7} cycloalkyl or R_3 and R_4 together with the nitrogen atom form a heterocyclic ring system; R_5 and/or R_6 are H, halo, CF_3, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} alkylthio or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring and R_7 and/or R_8 are H or C_{1-3} alkyl show therapeutic activity in the treatment of depression. Pharmaceutical compositions and processes for preparing compounds of formula I are disclosed.

SPECIFICATION

The Boots Company PLC therapeutic ag nts

This invention relates to compounds having useful therapeutic activity particularly but not exclusively as antidepressants, to pharmaceutical compositions containing such compounds and to processes for the preparation of such compounds.

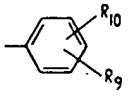
The present invention provides compounds of formula I



I

in which n=0 or 1;

in which, when n=0, R_1 is a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cyclo-alkyl group containing 3 to 7 carbon atoms, a cycloalkylalkyl group in which the cycloalkyl group contains 3 to 6 carbon atoms and the alkyl group contains 1 to 3 carbon atoms, an alkenyl group or an alkynyl group containing 2 to 6 carbon atoms or a group of formula II



II

in which R_9 and R_{10}, which may be the same or different, are H, halo or an alkoxy group containing 1 to 3 carbon atoms;

in which, when n=1, R_1 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_3 and R_4, which may be the same or different, are H, a straight or branched chain alky group containing 1 to 4 carbon atoms, an alkenyl group having 3 to 6 carbon atoms, an alkynyl group having 3 to 6 carbon atoms, a cycloalkyl group in which the ring contains 3 to 7 carbon atoms, a group of formula $R_{11}CO$ where R_{11} is H or R_3 and R_4 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring having 5 or 6 atoms in the ring which may contain further hetero atoms in addition to the nitrogen atom;

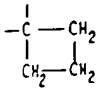
in which R_5 and R_6, which may be the same or different, are H, halo, trifluoromethyl, an alkyl group containing 1 to 3 carbon atoms, an alkoxy or alkylthio group containing 1 to 3 carbon atoms, phenyl, or R_5 and R_6, together with the carbon atoms to which they are attached, form a second benzene ring which may be substituted by one or more halo groups, an alkyl or alkoxy group containing 1 to 4 carbon atoms or the substituents of the second benzene ring together with the two carbon atoms to which they are attached may form a further benzene ring;

and in which R_7 and R_8 which may be the same or different are H or an alkyl group containing 1 to 3 carbon atoms;

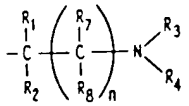
and their pharmaceutically acceptable salts.

In the formulae included in this specification the symbol

represents a 1,1-disubstituted cyclobutane group of formula



and $—CR_1R_2.(CR_7R_8.)_nNR_3R_4$ represents a group of formula



In the preferred compounds of formula I in which n=0, R_1 is a straight or branched chain alkyl group containing 1 to 4 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkyl-methyl group in which the cycloalkyl ring contains 3 to 6 carbon atoms or a group of formula II in which R_9 and/or R_{10} are H, fluoro or methoxy and in which R_2 is H or methyl. Examples of particularly preferred compounds of formula I are those in which when n=0 and R_2 is H, R_1 is methyl, ethyl, propyl,

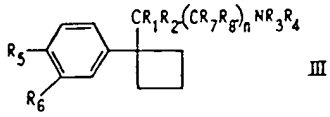
cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or phenyl.

In the preferred compounds of formula I in which n=1, R_1 is H or methyl, and R_2 is H. In particularly preferred compounds of formula I in which n=1 both R_1 and R_2 are H.

In preferred compounds of formula I, R_3 and/or R_4 are hydrogen, methyl, ethyl or formyl or, when R_3 and R_4 together with the nitrogen atom to which they are attached form a heterocyclic ring, the preferred compounds of formula I contain a heterocyclic group containing one nitrogen atom and 4 or 5 carbon atoms (e.g. pyrrolidinyl, piperidino) which is optionally substituted by one or more alkyl (e.g. methyl) groups (e.g. pyrrolidinyl substituted by two methyl groups), a heterocyclic group containing a second nitrogen atom which is optionally alkylated (e.g. 4-methylpiperazinyl) or a heterocyclic group including one or more double bonds (e.g. 1,2,3,6-tetrahydropyridyl). In particularly preferred compounds of formula I R_3 and/or R_4 are H, methyl, ethyl and formyl.

In preferred compounds of formula I R_5 and/or R_6 are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or R_5 and R_6 together with the carbon atom to which they are attached form a second benzene ring which may optionally be substituted by halo.

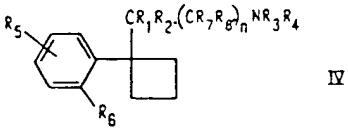
A first group of preferred compounds of formula I is represented by formula III



III

in which R_5 and R_6 are as defined above. In preferred compounds of formula III R_5 and R_6 which may be the same or different, are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or in which R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring which may optionally be substituted by a chloro group. In particularly preferred compounds of formula III R_5 and/or R_6 are H, fluoro, chloro, iodo, trifluoromethyl, methyl, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring which may optionally be substituted by a chloro group.

A second group of preferred compounds of formula I is represented by formula IV



IV

in which R_5 may be H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and in which R_6 is fluoro or methyl. In particularly preferred compounds of formula IV R_5 is H or chloro.

In preferred compounds of formula I in which n=1, R_7 is H, methyl or ethyl and R_8 is H and in particularly preferred compounds of formula I R_7 is H or ethyl and R_8 is H.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, maleates, acetates, citrates, fumarates, tartrates, succinates and salts with acidic amino acids such as aspartic and glutamic acids.

Compounds of formula I which contain one or more asymmetric carbon atoms can exist in different optically active forms. When R_1 and R_2 are different or R_7 and R_8 are different, the compounds of formula I contain a chiral centre. Such compounds exist in two enantiomeric forms and the present invention includes both enantiomeric forms and mixtures thereof. When both R_1 and R_2 are different and R_7 and R_8 are different, the compounds of formula I contain two chiral centres and the compounds exist in four diastereoisomeric forms. The present invention includes each of these diastereoisomeric forms and mixtures thereof.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier.

In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1—90% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oily suspensions. The excipients used in the preparation of these compounds are the excipients known in the pharmacists' art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by

known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous and oily media or sterile solutions in a suitable solvent.

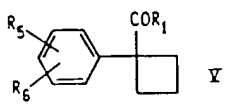
Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base.

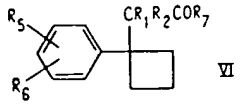
In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to tread depression in mammals including human beings. In such treatment the amount of the compound of formula I administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg.

Compounds of formula I in which R_4 is CHO may be prepared by the reductive amidation of ketones of formula V or of ketones or aldehydes of formula VI


V


VI

for example with formamide and formic acid or ammonium formate and formic acid to give compounds of formula I in which R_4 is CHO and R_3 is H or with formamides of formula $HCONHR_3$ in which R_3 is an alkyl or cycloalkyl group and formic acid or amines of formula R_3NH_2 in which R_3 is an alkyl or cycloalkyl group and formic acid.

Compounds of formula I in which R_4 is CHO may be prepared by the formylation of compounds of Formula I in which R_4 is H for example by reaction with methyl formate.

Compounds of formula I in which R_3 is other than H and R_4 is CHO may be prepared by reacting compounds of formula I in which R_3 is H and R_4 is CHO with a compound of formula R_3X where X is a leading group such as a halo group in the presence of a base.

Compounds of formula I may be prepared by the reductive amination of ketones of formula V or of ketones or aldehydes of formula VI. Examples of suitable reductive amination processes are given below:—

a) for compounds of formula I in which R_3 and R_4 and H, by reaction of the ketone or aldehyde with an ammonium salt for example ammonium acetate and a reducing agent such as sodium cyanoborohydride,

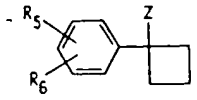
b) for compounds of formula I in which R_3 is alkyl or cycloalkyl and R_4 is H by reaction of the ketone or aldehyde with an amine of formula R_3NH_2 and a reducing agent such as sodium cyanoborohydride or sodium borohydride,

c) for compounds of formula I in which neither R_3 nor R_4 is hydrogen or in which R_3 and R_4 together with the nitrogen atom form a heterocyclic ring, by reaction of the ketone or aldehyde with an amine of formula HNR_3R_4 and either formic acid or a reducing agent such as sodium cyanoborohydride,

d) for compounds of formula I in which one or both of R_3 and R_4 are H or an alkyl or a cycloalkyl group or in which R_3 and R_4 together with the nitrogen atom form a heterocyclic ring, by catalytic hydrogenation at elevated temperature and pressure of a mixture of the ketone or aldehyde and an amine of formula HNR_3R_4.

Compounds of formula I in which R_3 and R_4 are both alkyl groups may be prepared by reacting a ketone of formula V or a ketone or aldehyde of formula VI with a dialkyl formamide of formula $HCONR_3R_4$ for example in the presence of formic acid.

Compounds of formula I may be prepared by the reduction of compounds of formula VII



VII

in which

a) Z is a group of formula $ICR_1{=}NOH$ or an ester or ether thereof to give compounds of formula I in which n=0 and R_2, R_3 and R_4 are H;

b) Z is a group of formula $—CR_1{=}NR_3$ (where R_3 is other than H or CHO) to give compounds of formula I in which n=0 and R_2 and R_4 are H;

c) Z is a group of formula $—CR_1{=}NY$ in which Y represents a metal-containing moiety derived from an organometallic reagent to give compounds of formula I in which n=0 and R_2, R_3 and R_4 are H;

d) Z is a group of formula $—CR_1R_2 . CN$ to give compounds of formula I in which n=1 and R_3, R_4, R_7 and R_8 are H;

e) Z is a group of formula $—CR_1R_2 . CR_7{=}NOH$ or an ester or ether thereof to give compounds of formula I in which n=1 and R_3, R_4 and R_8 are H;

f) Z is a group of formula $—CR_1R_2 . CR_7{=}NR_3$ (where R_3 is other than H or CHO) to give compounds of formula I in which n=1 and R_4 and R_8 are H;

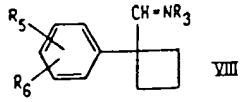
g) Z is a group of formula $—CR_1R_2 . CR_7{=}NY$ in which Y represents a metal-containing moiety derived from an organo-metallic reagent to give compounds of formula I in which n=1 and R_3, R_4 and R_8 are H;

h) Z is a group of formula $—CR_1R_2 . CONR_3R_4$ to give compounds of formula I in which n=1 and R_7 and R_8 are H.

Suitable reducing agents for the above reactions include sodium borohydride, sodium cyanoborohydride, lithium aluminium hydride or borane-dimethylsulphide complex.

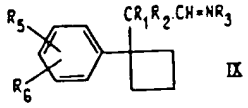
In (c) and (g) above Y is preferably MgBr derived from a Grignard reagent or Li derived from an organolithium compound.

Compounds of formula I in which n=0 may be prepared by the reaction of an organometallic reagent for example a Grignard reagent of formula R_1MgX where X is Cl, Br or I or an organolithium compound of formula R_1Li with imines of formula VIII



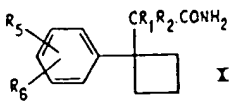
VIII

followed by hydrolysis to give secondary amines of formula I. In a similar manner imines of formula IX may be converted to secondary amines of formula I in which n=1

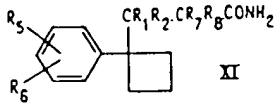


IX

Compounds of formula I in which R_3 and R_4 are H may be prepared by the decarboxylative rearrangement, for example using iodosobenzene-bistrifluoroacetate or by a Hofmann reaction using bromine in alkaline solution, of amides of formula X or amides of formula XI



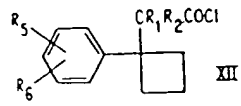
X



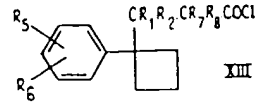
XI

to give amines of formula I in which n=0 and n=1 respectively.

Compounds of formula I in which R_3 and R_4 are H may be prepared by the decarboxylative rearrangement of acyl azides in the Curtius reaction. The acyl azides may be formed for example by reaction of acid chlorides of formula XII or acid chlorides of formula XIII with sodium azide

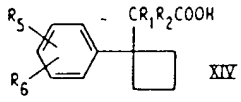


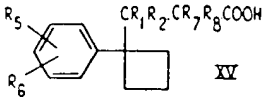
XII



XIII

Compounds of formula I in which R_3 and R_4 are H may be prepared by a Schmidt reaction in which


XIV


XV

Compounds of formula I in which R_4 is H may be prepared by hydrolysis of compounds of formula I in which R_4 is CHO, for example by acid hydrolysis.

Compounds of formula I in which R_4 is methyl may be prepared by reduction of compounds of formula I in which R_4 is CHO, for example by lithium aluminium hydride or by sodium bis(2-methoxyethoxy)aluminium hydride.

Compounds of formula I in which one or both of R_3 and R_4 is other than H may be prepared from compounds of formula I in which one or both of R_3 and R_4 are hydrogen by methods which are well known in the art for the conversion of primary to secondary or tertiary amines or for the conversion of secondary to tertiary amines. The following are given as examples of suitable processes:—

a) by alkylating primary amines of formula I to give secondary amines of formula I for example by a process which includes the steps of protecting the primary amine with a protecting group such as trifluoroacetyl, alkylating with an alkyl halide and removing the protecting group for example by hydrolysis;

b) by alkylating primary amines of formula I, for example, with an alkyl halide to give tertiary amines of formula I in which R_3 and R_4 are the same;

c) by alkylating secondary amines of formula I, for example, with an alkyl halide to give tertiary amines of formula I in which R_3 and R_4 may be different;

d) by reacting primary amines of formula I with sodium borohydride and acetic acid to give secondary amines of formula I in which R_3 is ethyl and R_4 is H;

e) by reacting primary amines of formula I with formaldehyde and formic acid to give tertiary amines of formula I in which both R_3 and R_4 are methyl

f) by reacting secondary amines of formula I in which R_4 is H with formaldehyde and formic acid to give tertiary amines of formula I in which R_4 is methyl

g) by formylating primary amines of formula I, for example by reaction with methyl formate, and reducing the resulting formamides, for example with lithium aluminium hydride to give secondary amines of formula I in which R_3 is methyl and R_4 is H;

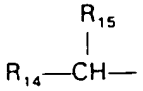
h) by formylating secondary amines of formula I, for example by reaction with methyl formate, and reducing the resulting formamides, for example with lithium aluminium hydride to give tertiary amines of formula I in which R_4 is methyl.

i) by acylating primary amines of formula I, for example by reaction with an acyl chloride of formula $R_{12}COCl$ or an anhydrde of formula $(R_{12}CO)_2O$ in which R_{12} is an alkyl, alkenyl or alkynyl group and reducing the resulting amides for example with lithium aluminium hydride to give secondary amines of formula I in which R_3 is $—CH_2R_{12}$ and R_4 is H.

j) by acylating secondary amines of formula I in which R_4 is H for example by reaction with an acyl chloride of formula $R_{12}COCl$ or an anhydride of formula $(R_{12}CO)_2O$ in which R_{12} is an alkyl, alkenyl or alkynyl group and reducing the resulting amides for example with lithium aluminium hydride

to give tertiary amines in which R_4 is CH_2R_{12};

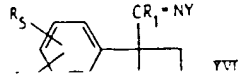
k) by reacting primary amines of formula I with an aldehyde of formula $R_{13}CHO$ in which R_{13} may be an alkyl group, an alkenyl or alkynyl group or a ketone of formula $R_{14}COR_{15}$ in which R_{14} and R_{15} which may be the same or different are an alkyl group, alkenyl group, alkynyl group or R_{14} and R_{15} together with carbon atom to which they are attached may form an alicyclic ring and reducing the resulting imines or enamines for example with sodium cyanoborohydride or, when R_{13}, R_{14} or R_{15} are not alkenyl or alkynyl, by catalytic hydrogenation to give secondary amines of formula I in which R_3 is $R_{13}CH_2—$ and



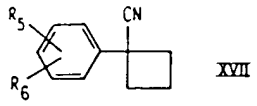
respectively;

l) by reacting primary amines of formula I with a non-geminally disubstituted alkane containing 2 or 3 carbon atoms between the carbon atoms carrying the substituents which may be for example halo preferably bromo, or *p*-toluenesulphonyloxy to give compounds of formula I in which R_3 and R_4 together with the nitrogen to which they are attached form a heterocyclic ring containing no heteroatoms other than the nitrogen atom.

The ketones of formula V may be prepared by the hydrolysis of imines of formula XVI


XVI

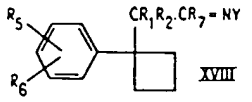
in which Y represents a metal-containing moiety derived from an organometallic reagent. The imines of formula XVI may be prepared by the reaction of said organometallic reagent with cyano compounds of formula XVII



XVII

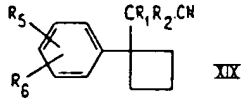
Suitable organometallic reagents include Grignard reagents of formula R_1MgX where X is Cl, Br or I (Y=MgX) and organolithium compounds of formula R_1Li (Y=Li).

The ketones of formula VI may be prepared by the hydrolysis of imines of formula XVIII



XVIII

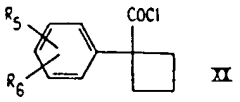
in which Y represents a metal-containing moiety derived from an organometallic reagent. The imines of formula XVIII may be prepared by the reaction of the said organometallic reagents with cyano compounds of formula XIX



XIX

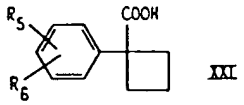
Suitable organometallic reagents include Grignard reagents of formula R_7MgX where X is Cl, Br or I (Y=MgX) and organolithium compounds of formula R_1Li (Y=Li).

Ketones of formula V may be prepared by the reaction of carboxylic acid derivatives such as an amide or acid halide with an organometallic reagent for example by the reaction of an acid chloride of formula XX



XX

with a Grignard reagent of formula R_1MgX where X is Cl, Br or I at low temperatures or by the reaction of a carboxylic acid of formula XXI

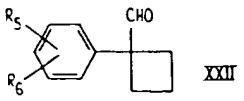


XXI

with an organometallic reagent, for example an organolithium compound of formula R_1Li.

Ketones of formula VI may be prepared by the reaction of carboxylic acid derivatives such as an amide or acid halide with an organometallic reagent for example by the reaction of an acid chloride of formula XII with a Grignard reagent of formula R_7MgX where X is Cl, Br or I at low temperatures or by the reaction of a carboxylic acid of formula XIV with an organometallic reagent for example an organolithium compound of formula R_7Li.

Ketones of formula V in which R_1 is alkyl (e.g. methyl) and ketones of formula VI in which R_7 is alkyl (e.g. methyl) may be prepared by the reaction of a diazoalkane (e.g. diazomethane) with aldehydes of formula XXII and VI respectively.



XXII

Aldehydes of formula VI may be prepared by methods well known in the art. The following are given as examples of suitable methods:—

a) by reduction of cyano compounds of formula XIX with for example di-*tert*-butylaluminium hydride or di-isobutylaluminium hydride.

b) by the reduction of carboxylic acid derivatives for example:—

i) by reduction of compounds of formula VII in which Z is $CR_1R_2CONR_3R_4$ and R_3 and R_4 are other than H for example by using lithium diethoxyaluminohydride.

ii) by reduction of amides formed by the reaction of ethyleneimine with an acid chloride of formula XII for example using lithium aluminium hydride as the reducing agent.

iii) by the reduction of acid chlorides of formula XII for example with lithium tri-*tert*-butoxy-aluminohydride.

c) by the oxidation of alcohols (prepared by the reduction of carboxylic acids of formula XIV) with, for example, chromium trioxide-pyridine complex in dichloromethane under anhydrous conditions.

Compounds of formula VII in which Z is a group of formula $—CR_1=NOH$ or $—CR_1R_2 . CR_7=NOH$ or ethers or esters thereof may be prepared by the reaction of hydroxylamine or an ether or ester thereof with ketones of formula V and ketones or aldehydes of formula VI respectively.

Compounds of formula VII in which Z is a group of formula $—CR_1=NR_3$ or $—CR_1R_2 . CR_7=NR_3$ may be prepared by the reaction of amines of formula NH_2R_3 with ketones of formula V and ketones or aldehydes of formula VI respectively.

The preparation of compounds of formula VII in which Z is a group of formula $—CR_1=NY$ or $—CR_1R_2 . CR_7=NY$ has been described above in respect of compounds of formula XVI and XVIII respectively.

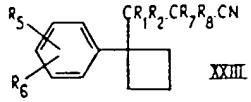
The preparation of compounds of formula VII in which Z is a group of formula $—CR_1R_2CN$ will be described hereinafter in respect of the cyano compounds of formula XIX.

Compounds of formula VII in which Z is a group of formula $—CR_1R_2CONR_3R_4$ may be prepared by the reaction of acid derivatives such as esters or acid halides (for example acid chlorides of formula XII) with amines of formula HNR_3R_4 or ammonia. Compounds of formula V in which Z is $CR_1R_2 . CONH_2$ may be prepared from cyano compounds of formula XIX for example by hydration, with aqueous acids or by reaction with hydrogen peroxide in the presence of a base.

Imines of formula VIII and IX may be prepared by reaction of amines of formula R_3NH_2 with aldehydes of formula XXII and VI respectively.

Amides of formula X may be prepared by the reaction of ammonia with carboxylic acid derivatives for example acid chlorides of formula XII or they may be prepared from cyano compounds of formula XIX for example by hydration with aqueous acids or by reaction with hydrogen peroxide in the presence of a base.

Amides of formula XI may be prepared by the reaction of ammonia with carboxylic acid derivatives for example acid chlorides of formula XIII or they may be prepared from cyano compounds of formula XXIII for example by hydration with aqueous acids or by reaction with hydrogen peroxide in the presence of a base.



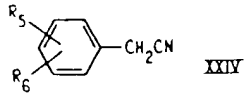
XXIII

Amides of formula X in which R_1 and R_2 are H and amides of formula XI in which R_7 and R_8 are H may be prepared from acid chlorides of formula XX and XII respectively by reaction with diazomethane to form a diazoketone which rearranges in the presence of ammonia and a catalyst for example silver to give the required amide.

Carboxylic acids of formula XIV, XV and XXI may be prepared by the hydrolysis, for example basic hydrolysis, of cyano compounds of formula XIX, XXIII and XVII respectively. Carboxylic acids of formula XIV and XV may be prepared by the reaction of amides of formula X and XI respectively with nitrous acid. Carboxylic acids of formula XXI may be prepared by the reaction of nitrous acid with the amides formed by the reaction of ammonia with carboxylic acid derivatives for example acid chlorides of formula XX or by the reaction of cyano compounds of formula XVII with hydrogen peroxide in the presence of a base.

Carboxylic acids of formula XIV in which R_1 and R_2 are H and carboxylic acids of formula XV in which R_7 and R_8 are H may be prepared from acid chlorides of formula XX and XII respectively by reaction with diazomethane to form diazoketones which rearranges in the presence of water and a catalyst for example silver to give the required acid.

Cyano compounds of formula XVII may be prepared by the reaction of cyano compounds of formula XXIV



XXIV

with a 1,3-disubstituted propane for example 1,3-dibromopropane and a base such as sodium hydride.

Cyano compounds of formula XIX in which R_1 and R_2 are H may be prepared from cyano compounds of formula XVII by for example the following series of reactions:—

a) hydrolysis of the cyano group to form a carboxylic acid of formula XXI;

b) reduction of the carboxylic acid for example with lithium aluminium hydride or borane-dimethylsulphide complex to form the corresponding alcohol;

c) replacement of the hydroxy group of the alcohol by a leaving group for example a *p*-toluene sulphonyloxy group and

In a similar manner cyano compounds of formula XXIII may be prepared from cyano compounds of formula XIX.

Cyano compounds of formula XIX in which one or both of R_1 and R_2 are other than H may be prepared from the corresponding cyano compounds of formula XIX in which R_1 and/or R_2 are H, for example by alkylation with an alkyl halide in the presence of a base such as lithium diisopropylamide. In a similar way cyano compounds of formula XXIII in which one or both of R_7 and R_8 are other than hydrogen may be prepared from compounds of formula XXIII in which R_7 and R_8 are both H.

Cyano compounds of formula XIX in which R_2=H may also be prepared by reacting ketones of formula V or an aldehyde of formula XXII with a reagent for introducing a cyano group such as p-toluenesulphonylmethyl isocyanide. In a similar manner cyano compounds of formula XXIII may be prepared from aldehydes or ketones of formula VI.

Acid chlorides of formula XX, XII and XIII may be prepared by the reaction of carboxylic acids of formula XXI, XIV and XV respectively with for example thionyl chloride.

Aldehydes of formula XXII may be prepared by methods well known to those skilled in the art. The following are given as examples of suitable methods:—

a) by the reduction of cyano compounds of formula XVII with for example di-*tert*-butylaluminium hydride or di-isobutylaluminium hydride.

b) by the reduction of carboxylic acid derivatives, for example

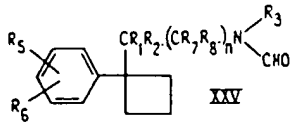
i) by the reduction of tertiary amides formed by the reaction of secondary amines with acid chlorides of formula XX for example when the secondary amine is a dialkylamine using lithium diethoxyaluminohydride as reducing agent or when the secondary amine is ethyleneimine using lithium aluminium hydride as the reducing agent,

ii) by the reduction of acid chlorides of formula XX for example with lithium tri-*tert*-butoxy-aluminohydride.

c) by the oxidation of alcohols (prepared by the reduction of carboxylic acids of formula XXI) with, for example chromium trioxide-pyridine complex in dichloromethane under anhydrous conditions.

Ketones of formula V (except those in which R_5 and R_6 are H and R_1 is methyl or ethyl), ketones of formula VI and aldehydes of formua VI (except those in which R_1, R_2, R_5 and R_6=H), the compounds of formula VII (except those in which Z=CR_1=NY and R_5 and R_6 are H and R_1 is methyl and ethyl), the imines of formula VIII (except those in which R_5 and R_6 are H), IX, XVI (except those in which R_5 and R_6 are H and R_1 is methyl or ethyl) and XVIII, the amides of formula X and XI, the carboxylic acids of formula XIV (except those in which R_1, R_2, R_5 and R_6 are H) and XV, the cyano compounds of formula XIX and XXIII and the acid chlorides of formula XII (except those in which R_1, R_2, R_5 and R_6 are H) and XIII which are described herein as intermediates are novel compounds. Some of cyano compounds of formula XVII and XXIV are novel compounds. Such novel compounds form a further aspect of the present invention.

Novel formamides of formula XXV



XXV

are described herein as intermediates, in the preparation of compounds of formula I and such novel formamides form a further aspect of the present invention.

The therapeutic activity of the compounds of formula I has been indicated by assessing the ability of the compounds to reverse the hypothermic effects of reserpine in the following manner. Male mice of the Charles River CDI strain weighing between 18 and 30 grammes were separated into groups of five and were supplied with food and water ad libitum. After five hours the body temperature of each mouse was taken orally and the mice were injected intraperitoneally with reserpine (5 mg/mg) in solution in deionised water containing ascorbic acid (50 mg/ml). The amount of liquid injected was 10 ml/kg of body weight. Nine hours after the start of the test food was withdrawn but water was still available ad libitum. Twenty-four hours after the start of the test the temperatures of the mice were taken and the mice were given the test compound suspended in a 0.25% solution of hydroxy ethyl cellulose (sold under the trade name Cellosize QP 15000 by Union Carbide) in deionised water at a dose volume of 10 ml/kg of body weight. Three hours later the temperatures of all the mice were again taken. The percentage reversal of the reserpine-induced loss of body temperature is then calculated by the formula:

$$\frac{\text{(Temperature after 27 hrs—Temperature after 24 hours)}}{\text{(Temperature after 5 hrs—Temperature after 24 hours)}} \times 100$$

The mean value for each group of five mice was taken at several dose rates to enable a value of the mean dose which causes a 50% reversal (ED50) to be obtained. All the compounds which are the final

by those skilled in the art that this test is indicative of compounds having anti-depressant activity in humans.

Table I lists compounds of formula I which gave a value of ED50 in the above test of 10 mg/kg or less.

Table I

1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N-methyl-1-[1-(2-naphthyl)cyclobutyl]ethylamine hydrochloride
N,N-dimethyl-1-[1-(4-chloro-3-trifluoromethylphenyl)cyclobutyl]ethylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine hydrochloride
1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride
N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride
1-[1-(4-biphenylyl)cyclobutyl]butylamine hydrochloride
N,N-dimethyl-1-[1-(4-biphenylyl)cyclobutyl]butylamine hydrochloride
1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine hydrochloride
N-formyl-1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine
1-[1-(3-chloro-4-methylphenyl)cyclobutyl]butylamine hydrochloride
N-formyl-1-[1-phenylcyclobutyl]butylamine
1-[1-(3-trifluoromethylphenyl)cyclobutyl]butylamine hydrochloride
1-[1-(naphth-2-yl)cyclobutyl]butylamine hydrochloride
1-[1-(6-chloronaphth-2-yl)cyclobutyl]butylamine
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]pentylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]pentylamine hydrochloride
N,N-dimethyl-1-[1-phenylcyclobutyl]-3-methylbutylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-formyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine
N,N-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(naphth-2-yl)cyclobutyl]-3-methylbutylamine hydrochloride
N-methyl-1-[1-(3,4-dimethylphenyl)cyclobutyl]-3-methylbutylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cyclopropyl)methylamine hydrochloride
N-methyl-[1-(4-chlorophenyl)cyclobutyl](cyclopentyl)methylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
N-methyl-[1-(4-chlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
[1-(3,4-dichlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
N-methyl-[1-(3,4-dichlorophenyl)cyclobutyl](cyclohexyl)methylamine hydrochloride
[1-(4-chlorophenyl)cyclobutyl](cycloheptyl)methylamine hydrochloride
1-[1-(4-chlorophenyl)cyclobutyl]-2-cyclopropylethylamine hydrochloride
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-2-cyclohexylethylamine hydrochloride
α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride
N-methyl-α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride
1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]butylamine
N,N-dimethyl-1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]butylamine hydrochloride
1-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}propylamine hydrochloride
N,N-dimethyl-1-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}propylamine hydrochloride
N,N-dimethyl-2-[1-(4-iodophenyl)cyclobutyl]ethylamine hydrochloride
N-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride
N,N-diethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride

The invention will now be illustrated by the following Examples which are given by way of example only. All compounds were characterised by conventional analytical techniques and gave satisfactory elemental analyses. All melting and boiling points are expressed in degrees Celsius.

Example 1

A solution of 3,4-dichlorobenzyl cyanide (25 g) and 1,3-dibromopropane (15 ml) in dry dimethyl

dispersed in mineral oil (7.5 g) and dimethylsulphoxide (200 ml) at a temperature in the range 30 to 35°C. The mixture was stirred at room temperature for two hours and propan-2-ol (8 ml) and then water (110 ml) were added dropwise. The mixture was filtered through a diatomaceous earth sold under the Registered Trade Mark Celite and the solid residue washed with ether. The ether layer was separated, washed with water, dried and evaporated. 1-(3,4-Dichlorophenyl)-1-cyclobutanecarbonitrile (b.p. 108—120°C at 0.15 Hg) was isolated by distillation. This method is a modification of that described by Butler and Pollatz (J. Org. Chem., Vol. 36, No. 9, 1971, p. 1308).

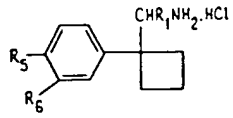
The 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile prepared as above (21.7 g) was dissolved in dry ether (50 ml) and the solution was added under nitrogen to the product of the reaction of gaseous methyl bromide with magnesium turnings (3.9 g) in dry ether (150 ml). The mixture was stirred at room temperature for two hours and then under reflux for two hours. Crushed ice and then concentrated hydrochloric acid (100 ml) were added and the mixture heated under reflux for two hours. The ether layer was separated, washed with water and aqueous sodium bicarbonate, dried and evaporated. 1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (b.p. 108—110° at 0.2 mm Hg) was isolated by distillation.

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (9.1 g) prepared as above, formamide (6.5 ml) and 98% formic acid (3 ml) were heated at 180°C for sixteen hours to give *N*-formyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine. Concentrated hydrochloric acid (20 ml) was added and the mixture heated under reflux for three hours. The solution was then cooled, washed with ether and sodium hydroxide solution added. The product was extracted with ether, and the ether extract washed with water, dried and evaporated. 1-[1-(3,4-Dichlorophenyl)cyclobutyl]ethylamine (b.p. 112—118° at 0.2 mm Hg) was isolated by distillation. The amine was dissolved in propan-2-ol and concentrated hydrochloric acid and the solution evaporated to dryness to give 1-[1-(3,4-dichlorophenyl)cyclobutyl]-ethylamine hydrochloride (m.p. 185—195°C). (Formula I n=0; R_1=Me; R_2, R_3 and R_4=H; R_5=4-Cl; R_6=3-Cl).

Example 1a

The preparation of *N*-formyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (m.p. 124—125°C) (Example 1(a) Formula I n=0; R_1=Me; R_2=H, R_3=H; R_4=CHO; R_5=4-Cl and R_6=3-Cl) described above was repeated and the product isolated by cooling the reaction mixture and collecting the solid produced by filtration. The formamide was then hydrolysed by concentrated hydrochloric acid in industrial methylated spirit to give the hydrochloride salt of 1-[1-(3,4-dichlorophenyl)-cyclobutyl]ethylamine.

In a similar manner to that described above in Example 1a the following compounds were prepared. The conditions for the hydrolysis of the formamides which were isolated by appropriate methods are shown in the footnotes.



Example	R_1	R_5	R_6	*b.p. (free base)*	*m.p. of HCl salt*	*Note*
1(b)	methyl	Cl	H	107°/1.2 mm Hg		A
1(c)	n-butyl	Cl	H		138—139°	B
1(d)	methyl	I	H		205—207°	C
1(e)	methyl	Cl	CF_3		216—217°	D

A. aqueous HCl/industrial methylated spirit

B. The 1-valeryl-1-(4-chlorophenyl)cyclobutane was prepared in tetrahydrofuran. Hydrolysis was performed using concentrated HCl/industrial methylated spirit.

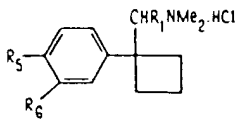
C. concentrated HCl/diethyleneglycoldimethyl ether (in a similar manner to that described later in Example 12).

D. concentrated HCl/industrial methylated spirit.

Example 2

The product of Example 1 (4.04 g), water (0.5 ml) and 98% formic acid (3.6 ml) were mixed with cooling. 37—40% Aqueous formaldehyde (3.8 ml) was added and the solution was heated at 85—95°C for five hours. The solution was evaporated to dryness and the residue acidified with concentrated hydrochloric acid and the water removed by repeated addition of propan-2-ol followed by evaporation *in vacuo*. Crystals of *N,N*-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 211—213°C) (Formula I n=0; R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=3-Cl) were isolated.

In a similar way to that described above the compounds of Example 1(b) and 1(d) were converted into the compounds listed below.



Example	Starting material	R_1	R_5	R_6	m.p. of HCl salt	b.p. of free base
2(a)	1(b)	methyl	Cl	H		98—100°/0.5 mm
2(b)	1(d)	methyl	I	H	260—261°	

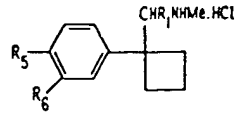
Example 3

In a similar manner to that described above in Examples 1 and 2 *N,N*-dimethyl-1-[1-(4-biphenyl)-cyclobutyl]ethylamine hydrochloride (m.p. 196—197°C) was prepared. (Formula I n=0; R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-phenyl and R_6=H).

Example 4

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (15 g) prepared as described in Example 1, *N*-methylformamide (47.5 ml) 98% formic acid (10.3 ml) and a 25% aqueous solution of methylamine (1.5 ml) were mixed and heated with stirring at 170—180° for eight hours. The mixture was cooled and extracted with ether. The ether extract was washed, dried and evaporated to yield a light yellow oil which was heated under reflux with concentrated hydrochloric acid (50 ml) for two hours. Industrial methylated spirit (IMS) (50 ml) was added and the mixture heated under reflux for sixteen hours. The mixture was then cooled to 0°C and the white precipitate collected by filtration, washed with acetone and dried. The product, *N*-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride, had a melting point of 254 to 256°C (Formula I n=0; R_1=Me; R_2=H; R_3=Me; R_4=H; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds of formula I were prepared



Example	R_1	R_5	R_6	b.p. of amine	m.p. of HCl salt	Note
4(a)	Me	Cl	H	98—100°/0.15 mm	240—241°	
4(b)	Me	H	Cl		269—272°	
4(c)	Me	Br	H	96—98°/0.1 mm		
4(d)	Me	H	Br		251—255°	
4(e)	Me	CF_3	H		219—221°	
4(f)	Me	H	CF_3		225—228°	
4(g)	Me	—(CH=CH)$_2$—			254—257°	
4(h)	Me	Cl	CF_3		198—200°	
4(i)	Et	Cl	H		238—240°	
4(j)	Pr	Cl	H		228—229°	A
4(k)	Bu	Cl	H		152—153°	A
4(l)	Me	I	H		242—243°	

Note A: The starting ketone was prepared in tetrahydrofuran as reaction solvent in place of ether.

Example 5

A mixture of 70% aqueous ethylamine (50 ml) and water (100 ml) was gradually mixed with a mixture of 98% formic acid (50 ml) and water (100 ml) to give a neutral solution which was evaporated at 100°C/100 mm Hg until 180 ml of water had been collected. The residue was heated to 140°C and 1-acetyl-1-(4-chlorophenyl)cyclobutane (10.4 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane and 98% formic acid (10 ml) were added. The mixture was heated on an oil bath at a temperature of 180—200°C for sixteen hours. The mixture was distilled until an internal temperature of 170°C was obtained and this temperature was maintained for two hours. Any volatile material was removed by distillation at 160°C/20 mm and the residue heated under reflux with concentrated hydrochloric acid (15 ml) and industrial methylated spirit (IMS) (15 ml) for three hours. The IMS was evaporated on a rotary evaporator and the residue washed with ether. The aqueous phase was brought to pH 12 with sodium hydroxide and extracted with ether. The ether extract was dried and on evaporation yielded a residue which was treated with aqueous hydrochloric acid to give *N*-ethyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 203—205°C) (Formula I n=0; R_1=Me; R_2=H; R_3=Et; R_4=H; R_5=4-Cl; R_6=H).

Example 6

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (15 g) prepared in a similar manner to the 1-(3,4-

dichlorophenyl)cyclobutanecarbonitrile of Example 1 in dry ether (50 ml) was added to the product of the reaction between magnesium turnings (3.18 g) and propyl bromide (15.99 g) in dry ether (50 ml). The ether was replaced by tetrahydrofuran and the mixture heated with stirring under reflux for eighteen hours. The mixture was cooled and ice and then concentrated hydrochloric acid (52 ml) added. The resulting mixture was stirred under reflux for ten hours and extracted with ether. The ether extract yielded a residue from which 1-butyryl-1-(4-chlorophenyl)cyclobutane (b.p. 106—108°/0.3 mm Hg) was distilled.

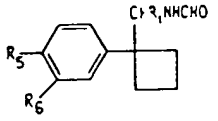
A mixture of the ketone produced as described above (21 g) and 98% formic acid (6 ml) was added over a period of one and a half hours to formamide (15 mp) at 160°C. After completion of the addition the temperature was raised to 180 to 185°C and maintained in this range for five hours. The mixture was cooled and extracted with chloroform to yield a thick gum which on heating with petroleum ether (b.p. 60—80°) gave a colourless solid which was recrystallised from petroleum ether (b.p. 60—80°) to yield *N*-formyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine (m.p. 97.5 to 98.5°C) (Formula I n=0; R_1=propyl; R_2=H; R_3=H; R_4=CHO; R_5=4-Cl; R_6=H).

Example 7

A solution of 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile prepared as described in Example 1 (35.2 g) in ether (100 ml) was added to a solution of propyl magnesium bromide prepared by the reaction of propyl bromide (32 g) with magnesium turnings (6.36 g) in ether (100 ml). The ether was replaced by dry toluene and the mixture heated under reflux for one hour. Water (200 ml) and then concentrated hydrochloric acid (120 ml) were added and the mixture heated under reflux for one hour. The reaction mixture was extracted with ether and after washing and drying the extract yielded a residue from which 1-butyryl-1-(3,4-dichlorophenyl)cyclobutane (b.p. 120—128°C at 0.25 mm) was distilled.

The ketone produced as described above (37.0 g) and 98% formic acid (9 ml) were added to formamide (23.5 ml) at 170°C and the temperature kept at 175—180°C for five hours. A further portion of formic acid (4.5 ml) was added and the mixture was maintained at 175—180°C for a further fifteen hours. The mixture was extracted with ether which on evaporation gave a thick oil which was crystallised from petroleum ether (b.p. 60—80°) to give *N*-formyl-1-[1-(3,4-dichlorophenyl)-cyclobutyl]butylamine having a melting point of 103—105°C (Formula I n=0; R_1=propyl; R_2=H; R_3=H; R_4=CHO; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were made

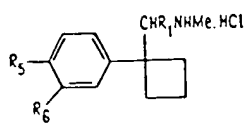


Example	R_1	R_5	R_6	*m.p. (°C)*
7(a)	isobutyl	Cl	H	110—112°
7(b)	propyl	Cl	F	115—116°
7(c)	phenyl	Cl	H	94—96°
7(d)	propyl	H	H	98—102°

Example 8

The product of Example 7 (4.0 g) in dry tetrahydrofuran (25 ml) was added rapidly to a stirred mixture of lithium aluminium hydride (1.4 g) in dry tetrahydrofuran (25 ml) under nitrogen. The mixture was heated under reflux for five hours and then cooled. Water (15 ml) and then 10% sodium hydroxide solution (3 ml) were added and the mixture filtered through diatomaceous earth sold under the Registered Trade Mark Celite. The product was extracted into ether, back extracted into 5N hydrochloric acid and the aqueous layer was basified and extracted with ether. The ether extract yielded an oil which was dissolved in propan-2-ol (5 ml) and concentrated hydrochloric acid was added to pH 2. Evaporation of the resulting solution gave a white solid which was collected, washed with acetone and dried. The product was *N*-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride and had a melting point of 234—235°C (Formula I n=0; R_1=propyl; R_2=H; R_3=H; R_4=Me; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were prepared

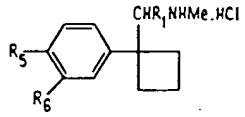


Example	R_1	R_5	R_6	*m.p. (°C)*
8(a)	phenyl	Cl	H	275—278°

Exampl 9

The product of Example 7 (10 g) in solution in ether (50 ml) was added to a 70% toluene solution of sodium bis-(2-methoxyethoxy)aluminium hydride sold under the trade mark Red-al (40 ml) at a temperature in the range 25 to 30°C. The mixture was stirred at this temperature for four hours. Water (25 ml) was added dropwise with cooling and the mixture filtered through diatomaceous earth (Celite). Aqueous NaOH was added and an ether extraction performed. The ether extract was washed with water and back extracted with 5N hydrochloric acid. A white solid (m.p. 232—235°C) appeared at the interface which was collected. Base was added to the aqueous phase and a further ether extraction performed. Evaporation of the ether extract yielded an oil which was dissolved in propan-2-ol (5 ml) and concentrated hydrochloric acid added to pH 2. Evaporation to dryness gave a white solid (m.p. 233—236°C). The white solids were combined and recrystallised from propan-2-ol to yield N-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 236—237°C) (Formula I n=0; R_1=propyl; R_2=H; R_3=H; R_4=Me; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were prepared. Where the formyl starting material was insoluble in ether, a solution of the reducing agent was added to a stirred suspension of the formyl compound. As the size of the group R_1 is increased the hydrochloride salts of the desired compounds become less soluble in the aqueous phase and more soluble in the organic phase so that appropriate modifications in the isolation procedure are required as will be apparent to those skilled in the art.



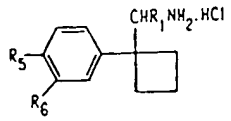
Example	R_1	R_5	R_6	*m.p.*
9(a)	isopropyl	Cl	H	257—259°
9(b)	*sec*-butyl	Cl	H	209—212°
9(c)	isobutyl	Cl	H	225—233°
9(d)	cyclopentyl	Cl	H	252—256°
9(e)	n-hexyl	Cl	H	117—118°
9(f)	4-methoxyphenyl	Cl	H	264—266°
9(g)	3-methoxyphenyl	Cl	H	254—255°
9(h)	2-methoxyphenyl	Cl	H	149—153°
9(i)	cyclohexyl	Cl	H	170—172°
9(j)	isobutyl	—(CH = CH)$_2$—		256—259°
9(k)	cyclohexyl	Cl	Cl	223—224°
9(l)	isobutyl	Me	Me	(1)
9(m)	propyl	OMe	H	173—175°
9(n)	methyl	phenyl	H	116—118°

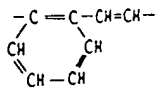
(1) Boiling point of free base >150° at 1.0 mm Hg.

Example 10

The product of Example 7 (4 g), diethyleneglycoldimethyl ether (25 ml), water (10 ml) and concentrated hydrochloric acid (10 ml) were mixed and heated under reflux for nine hours. The solution was washed with ether and aqueous NaOH added before an ether extraction was performed. The ether extract was washed with brine and water and yielded an oil on evaporation. The oil (3.19 g) was dissolved in a mixture of propan-2-ol (4 ml) and ether (20 ml) and concentrated hydrochloric acid (1.5 ml) added. The solvent was evaporated *in vacuo*. Repeated dissolution in industrial methylated spirit and evaporation *in vacuo* gave a gum which solidified on warming *in vacuo*. The product was recrystallised from petroleum ether (b.p. 100—120°C) and had a melting point of 201—203°C. The product was 1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (Formula I n=0; R_1=propyl; R_2=H; R_3, R_4=H; R_5=4-Cl and R_6=3-Cl).

In a similar manner to that described above the following compounds were prepared. As the size of the group R_1 is increased the hydrochloride salts of the desired compounds become less soluble in the aqueous phase and more soluble in the organic phase so that appropriate modifications in the isolation procedure are required as will be apparent to those skilled in the art.



Example	R_1	R_5	R_6	m.p.
10(a)	isopropyl	Cl	H	200—202°
10(b)	*sec*-butyl	Cl	H	178—179°
10(c)	isobutyl	Cl	H	163—165°
10(d)	cyclopentyl	Cl	H	185—210° (dec)
10(e)	phenyl	Cl	H	271—276°
10(f)	4-methoxyphenyl	Cl	H	214—219°
10(g)	cyclohexyl	Cl	H	206—210°
10(h)	isobutyl	H	H	210—212°
10(i)	cyclopropyl	Cl	H	204—206°
10(j)	propyl	pH	H	235—236°
10(k)	propyl	Me	Cl	214—217°
10(l)	propyl	—(CH=CH)$_2$—		157—159°
10(m)	cycloheptyl	Cl	H	156—162°
10(n)	cyclohexyl	Cl	Cl	215°
10(p)	methyl	Cl	F	215—217°
10(q)	propyl	OMe	H	178—179°
10(r)	propyl	Cl	F	186—188°
10(s)	propyl	Cl	H	174—175°
10(t)	cyclohexylmethyl	Cl	H	148—150°
10(u)	cyclopropylmethyl	Cl	H	184—185°
10(v)	propyl	—CH=CH—CCl=CH—		(a)
10(w)	propyl	H	CF_3	126—128°
10(x)	4-fluorophenyl	Cl	H	279°
10(y) (b)	methyl			248—262°

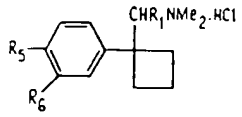
(a) boiling point of free base 168°C/0.05 mm Hg.
(b) diethyleneglycoldimethyl ether replaced by ethyleneglycoldimethyl ether.

In a similar manner to that described above, 1-[1-(4-chloro-2-fluorophenyl)cyclobutyl]-butylamine (b.p. 99°C/0.05 mm). (Formula I n=0; R_1=propyl; R_2, R_3 and R_4=H; R_5=4-Cl; R_6=2-F), 1-[1-(2-fluorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 175—177°C). Formula I n=0; R_1=propyl; R_2, R_3, R_4, R_5=H and R_6=2-F) and 1-[1-(4-chloro-2-methyl)cyclobutyl]butylamine hydrochloride (m.p. 188—190°C) (Formula I n=0; R_1=propyl; R_2, R_3 and R_4=H; R_5=4-Cl and R_6=2-Me) were prepared as Examples 10(z), 10(aa) and 10(bb) respectively.

Example 11

The product of Example 10(c) (3.3 g) in the form of the free base, formic acid (2.99 g) and water (1 ml) were mixed with cooling. 37—40% Aqueous formaldehyde (3.93 ml) was added and the mixture heated for eighteen hours at a temperature of 85—95°C. Excess dilute hydrochloric acid was added and the solution evaporated to dryness. The residue was basified with 5N sodium hydroxide solution and the product was extracted into ether. Evaporation of the ether yielded a pale yellow oil which was dissolved in a mixture of propan-2-ol (4 ml) and ether (20 ml) and concentrated hydrochloric acid (2 ml) was added dropwise. The solution was evaporated and the residue dissolved repeatedly in ethanol and evaporated *in vacuo* to give a gum which was triturated with petroleum ether (b.p. 60—80°) to yield a yellow solid which was recrystallised from acetone. The product was *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride (m.p. 195—197°C). (Formula I n=0; R_1=isobutyl; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=H).

In a similar manner to that described above the following compounds of Formula I were prepared



Example	Starting material	R_1	R_5	R_6	m.p.
11(a)	10(h)	isobutyl	H	H	195—198°
11(b)	10(j)	propyl	Ph	H	194—196°
11(c)	10(n)	cyclohexyl	Cl	Cl	227—228°
11(d)	10(q)	propyl	OMe	H	187—188°
11(e)	10(s)	propyl	Cl	H	194—196°
11(f)	10(t)	cyclohexyl methyl	Cl	H	194—196°
11(g)	10(u)	cyclopropyl methyl	Cl	H	165—167°
11(h)	10(v)	propyl	—CH=CH—CCl=CH—		(a)
11(i)	——	isobutyl	Cl	Cl	225—226°
11(j)	10(x)	4-fluorophenyl	Cl	H	234°
11(k)	——	propyl	isopropyl	H	211—213°

(a) boiling point of free base <250°C/0.05 mm Hg.

Example 11(l)

In a similar manner to that described above *N,N*-dimethyl-1-[1-(4-chloro-2-fluorophenyl)-cyclobutyl]butylamine hydrochloride (m.p. 183°) was prepared. (Formula I n=0; R_1=propyl; R_2=H; R_3 R_4=Me; R_5=4-Cl; R_6=2-F).

Example 12

The product of Example 7 (8.3 g), diethyleneglycol-dimethyl ether (50 ml), water (20 ml) and concentrated hydrochloric acid (20 ml) were mixed and heated under reflux for sixteen hours. The mixture was poured into water, aqueous NaOH was added and the product extracted into ether. Evaporation gave a dark oil. A sample of this oil (7.9 g), water (0.7 ml) and formic acid (6.5 ml) were mixed and formaldehyde (6.5 ml) added. The mixture was heated under reflux for three hours and then concentrated hydrochloric acid (10 ml) and propan-2-ol (10 ml) were added. Evaporation to dryness gave *N,N*-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine hydrochloride (m.p. 195—196°) as a white solid (Formula I n=0; R_1=propyl; R_2=H; R_3, R_4=Me; R_5=4-Cl and R_6=3-Cl).

Example 13

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (37.6 g) prepared in a similar manner to the 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile described in Example 1 was added to a solution of potassium hydroxide (32.4 g) in diethyleneglycol (370 ml) and the mixture heated under reflux for three and a half hours. The reaction mixture was poured into an ice/water mixture and the resulting solution was washed with ether. The aqueous layer was added to a mixture of concentrated hydrochloric acid (100 ml) and ice and the resulting precipitate of 1-(4-chlorophenyl)-1-cyclobutanecarboxylic acid (m.p. 86—88°) collected, washed with water and dried.

A solution of the acid (10.5 g) prepared as above in tetrahydrofuran (150 ml) was added dropwise under nitrogen to a stirred suspension of lithium aluminium hydride (2 g) in tetrahydrofuran (150 ml). The mixture was stirred under reflux for two hours and water added. The mixture was filtered through diatomaceous earth (Celite-RTM) and the product extracted into ether. After washing with water and drying, the ether was evaporated to give a residue which was recrystallised from petroleum ether (b.p. 60—80°). The product was 1-[1-(4-chlorophenyl)cyclobutyl]methyl alcohol (m.p. 60—62°C).

A solution of the alcohol prepared as described above (60 g) in pyridine (52 ml) was added dropwise to a solution of p-toluenesulphonylchloride (60 g) in pyridine (100 ml) cooled in ice. The temperature was allowed to rise to room temperature and remain there for eighteen hours. 1-[1-(4-Chlorophenyl)cyclobutyl]methyl p-toluene sulphonate (m.p. 99—100°C) was precipitated by pouring the reaction mixture into a mixture of ice and concentrated hydrochloric acid (200 ml).

A solution of the sulphonate compound (97 g) prepared as described above and sodium cyanide (16.6 g) in dimethyl sulphoxide (370 ml) was heated on a steam bath for eighteen hours. The mixture was poured into water and extracted with ether. After washing and drying the ether was evaporated to leave a solid residue of 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile (m.p. 63—65°C).

A solution of di-isopropylamine (16.5 g) in dry tetrahydrofuran (50 ml) was stirred under nitrogen at a temperature of 0°C and a 1.6 M solution of n-butyllithium in hexane (100 ml) added dropwise. The

was added dropwise. The temperature of the mixture was allowed to rise to 0°C and the mixture was stirred for ten minutes before a solution of methyl iodide (10 ml) in tetrahydrofuran (10 ml) was added. Tetrahydrofuran (75 ml) was added to give a homogeneous solution and a further solution of methyl iodide (4 ml) in tetrahydrofuran (10 ml) added. The mixture was stirred at ambient temperature for two hours and then water (50 ml) added. The aqueous phase was washed with ether and the ether combined with the organic phase of the reaction mixture. The combined organic phases were washed three times with 5N hydrochloric acid, three times with water, dried and evaporated to yield an oil which solidified and was recrystallised from industrial methylated spirit to give 2-[1-(4-chlorophenyl)-cyclobutyl]-2-methylpropionitrile (m.p. 73—75°C).

The nitrile prepared above (4 g) was heated under reflux with potassium hydroxide (8 g) in diethyleneglycol (40 ml) for 24 hours. The reaction mixture was cooled, added to water (50 ml) and the aqueous phase washed twice with ether. The aqueous phase was acidified with 5N hydrochloric acid and extracted with three portions of ether. The combined ether extracts were washed with water, dried and evaporated to give a white solid which was recrystallised from petroleum ether (b.p. 60—80°) to give 2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropionic acid (m.p. 95—110°C).

Oxalyl chloride (10 ml) was added to the acid (2 g) prepared as above and after the initial effervescence had subsided the mixture was heated under reflux for one hour. Excess oxalyl chloride was removed by distillation and the residual oil added to concentrated aqueous ammonia (75 ml). An oily solid formed which was extracted into ethyl acetate. The extract was washed with water, dried and evaporated to give 2-[1-(4-chlorophenyl)cyclobutyl]-2-methyl propionamide.

The amide prepared as above (1.34 g) was dissolved in a mixture of acetonitrile (8 ml) and water (8 ml) and iodosobenzene bistrifluoroacetate (3.4 g) added and the mixture stirred at ambient temperature for five and a half hours. Water (75 ml) and concentrated hydrochloric acid (8 ml) were added and the mixture extracted with ether. The ether extract was washed with 5N hydrochloric acid and the aqueous phase basified and extracted with further portions of ether which were dried and evaporated to give an oil. The oil was dissolved in petroleum ether (b.p. 80—100°) and dry hydrogen chloride gas passed through the solution. 1-[1-(4-Chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 257—259°C) was collected by filtration (Formula I n=0; R_1, R_2=Me; R_3, R_4=H; R_5=4-Cl; R_6=H).

Example 14

The product of Example 4(h) (3.4 g) was mixed with anhydrous sodium formate (0.72 g), 98% formic acid (10 ml) and 37—40% aqueous formaldehyde solution (5 ml) and the mixture heated at a temperature of 85—95°C for sixteen hours. The mixture was diluted with water (50 ml) and basified to pH 10 with aqueous sodium hydroxide solution. The basic aqueous solution was extracted with ether, washed with water and dried with magnesium sulphate. Dry hydrogen chloride gas was bubbled through the ether extract to give a white precipitate of *N,N*-dimethyl-1-[1-(4-chloro-3-trifluoromethyl-phenyl)cyclobutyl]ethylamine hydrochloride (m.p. 246—247°C) (Formula I n=0; R_1=Me; R_2=H; R_3, R_4=Me; R_5=4-Cl and R_6=3-CF_3).

Example 15

The production of salts of the compounds of the invention is illustrated by the following Examples in which equimolar amounts of the base and the acid were taken up in a solvent. The salt was then obtained from the solution by conventional techniques.

Example	*Base*	*Acid*	*Solvent*	*m.p. of salt*
15(a)	10(s)	citric	aqueous acetone	158—160°
15(b)	10(s)	maleic	ether	155—157°
15(c)	10(s)	succinic	ether	152—155°
15(d)	2	L(+)tartaric	I.M.S.	150—153°
15(e)	Note (a)	citric	ether/methanol	163—164° (dec)

(a) The base was 1-[1-(3,4-dimethylphenyl)cyclobutyl]-3-methylbutylamine prepared in a similar manner to that described in Example 10.

Example 16

A solution of bromobenzene (15.7 g) in ether (50 ml) was added dropwise with cooling to magnesium turning (2.4 g) under an atmosphere of nitrogen. A solution of 1-(4-chlorophenyl)-cyclobutanecarbonitrile (19.1 g) prepared in a similar manner to that described in Example 1 for the 1-(3,4-dichlorophenyl)cyclobutane carbonitrile in ether (50 ml) was added and the ether replaced by dry toluene (130 ml). The reaction mixture was heated on a steam bath for one hour. A sample (20 ml) of the resulting solution was added to a solution of sodium borohydride (1 g) in diethyleneglycoldimethyl ether (60 ml) and the mixture was stirred for one and a half hours. Water (60 ml) was added slowly and the aqueous layer extracted with toluene. The toluene extracts were washed with water, dried and

added and the solution filtered and evaporated. Trituration with dry acetone gave α-[1-(4-chlorophenyl)cyclobutyl]benzylamine hydrochloride (m.p. 277—279°C) (Formula I n=0; R_1=Ph; R_2=H; R_3, R_4=H; R_5=4-Cl; R_6=H).

Example 17

Methyl formate (62 ml) was added dropwise to isopropylamine (85.5 ml) with stirring at a rate which maintained gentle reflux conditions. Stirring was continued for two hours after the addition. Methanol was distilled off at 100°C and *N*-isopropylformamide (b.p. 108—109°C/25 mm Hg) obtained by distillation.

1-Acetyl-1-(4-chlorophenyl)cyclobutane (10.4 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane and 98% formic acid (5 ml) were added to N-isopropylformamide (43.5 g) and the mixture heated at 180°C for four hours. Excess starting material was distilled off under reduced pressure (20 mm Hg) to leave a viscous residue which was heated under reflux with concentrated hydrochloric acid (30 ml) for six hours. The reaction mixture was washed with ether until a colourless solution was obtained. The aqueous phase was basified, extracted with ether, dried and evaporated to give an oil which was dissolved in 5N hydrochloric acid. On evaporation a yellow oil was obtained which was triturated with petroleum ether (b.p. 62—68°C) to give *N*-isopropyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 170—174°C) (Formula I n=0; R_1=Me; R_2=H; R_3=isopropyl; R_4=H; R_5=4-Cl; R_6=H).

Example 18

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane (7.0 g) prepared as described in Example 1 was slowly added to a mixture of pyrrolidine (25 ml) and 98% formic acid (15 ml) heated to 130—135°C for five hours. The mixture was stirred and heated at 160—165°C for sixteen hours. After cooling the mixture was poured into 5N hydrochloric acid (200 ml). The solution was washed with ether, basified with aqueous sodium hydroxide solution and extracted with ether. The ether extract was washed with water, dried and hydrogen chloride gas was passed into the extract which was then evaporated to dryness. The residue was triturated with dry ether to give a solid which was recrystallised from propan-2-ol to give *N*-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethyl pyrrolidine hydrochloride (m.p. 233—235°C) (Formula I n=0; R_1=Me; R_2=H; R_3 and R_4 together with the nitrogen to which they are attached form a pyrrolidine ring; R_5=4-Cl and R_6=3-Cl).

Example 19

1-(4-Chlorophenyl)-1-cyclobutane carboxylic acid (10.5 g) prepared as described in Example 13 was heated under reflux with thionyl chloride (20 ml) for $2\frac{1}{2}$ hours. Excess thionyl chloride was evaporated off and the acid chloride of the above acid distilled (b.p. 82—96°/0.2 mm Hg).

A solution of the acid chloride (23.0 g) in dry tetrahydrofuran (100 ml) was added slowly to the product of the reaction of magnesium turnings (3.0 g) and ethyl bromide (12.0 g) in dry tetrahydrofuran at a temperature of −70 to −60°C. The temperature was kept at −60°C for an hour and was then allowed to rise to 0°C. Water (50 ml) was added followed by 5N hydrochloric acid (150 ml) with cooling. The reaction mixture was extracted with ether, washed with water, sodium bicarbonate solution, dried. The solvent was removed by evaporation and 1-propionyl-1-(4-chlorophenyl)-cyclobutane obtained by distillation (b.p. 96—104°C/0.25 mm).

The ketone produced above was converted to *N*,*N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl-propylamine hydrochloride (m.p. 213—215°C) in a similar manner to that described in Example 12 (Formula I n=0; R_1=Et; R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=H).

Example 20

1-Acetyl-1-(4-chlorophenyl)cyclobutane (61 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane, platinum oxide (0.75 g), 33% solution of methylamine in ethanol (60 g) and ethanol (30 ml) were charged into an autoclave. The autoclave was filled with hydrogen and maintained at about 60°C and 20 bar pressure for ten hours. The reaction mixture was filtered through charcoal and the solids washed with absolute alcohol. The solvents were removed by evaporation and a sample of the residue (10 g) was shaken with 2M hydrochloric acid (50 ml) and ether (50 ml). The aqueous layer was basified and extracted with ether. The ether extract yielded a liquid on evaporation which was distilled (109°C/0.3 mm Hg) to give *N*-methyl-1-[1-(4-chlorophenyl)cyclobutyl]ethylamine (Formula I n=0; R_1=Me; R_2=H; R_3=Me; R_4=H; R_5=4-Cl and R_6=H).

Example 21

Sodium borohydride (2.0 g) was added to solution of 1-[1-(3,4-dichlorophenyl)cyclobutyl]-ethylamine (1.5 g prepared by treating the product of Example 1 with aqueous sodium hydroxide) in glacial acetic acid (30 ml). The mixture was heated at 95—100°C for sixteen hours and then cooled. Aqueous sodium hydroxide solution was added and the reaction mixture extracted with ether. The ether extract was shaken with 5N hydrochloric acid and the aqueous layer was washed with ether, basified and extracted with ether. Hydrogen chloride gas was passed into the ether extract which was

ethylamine hydrochloride (m.p. 211—212°C). (Formula I n=0; R_1=Me; R_2=H; R_3=Et; R_4=H; R_5=4-Cl and R_6=3-Cl).

Example 22

A mixture of *N*-ethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (0.5 g prepared by treating the product of Example 21 with aqueous sodium hydroxide) and acetic anhydride (1 ml) was heated at 40—45°C for thirty minutes. The reaction mixture was basified and extracted with ether. The ether extract was washed, dried and evaporated to give *N*-acetyl-*N*-ethyl-1-[1-(3,4-dichlorophenyl)-cyclobutyl]ethylamine as an oil.

This oil was dissolved in tetrahydrofuran (10 ml) and borane-dimethylsulphide complex (0.5 ml) added dropwise. The reaction mixture was stirred at room temperature for two hours and then heated to 35—40°C for thirty minutes. After cooling the reaction mixture was basified and extracted with ether. Hydrogen chloride gas was passed into the dried ether extract which was evaporated to dryness. Trituration with ether gave *N,N*-diethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 199—201°C). (Formula I n=0; R_1=Me; R_2=H; R_3, R_4=Et; R_5=4-Cl and R_6=3-Cl).

Example 23

A mixture of 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane (2.2 g) prepared as described in Example 1, ammonium acetate (7 g), sodium cyanoborohydride (0.4 g) and methanol (28 ml) was stirred at room temperature for four days. The reaction mixture was poured into a mixture of ice and water and the resulting mixture extracted with ether. The ether extract was washed with water, dried and the ether removed to leave 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine as an oil which was identified by standard analytical techniques as the compound of Example 1 in the form of its free base.

Example 24

A mixture of 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane (4.26 g) prepared as described in Example 1, hydroxylamine hydrochloride (1.6 g), sodium acetate trihydrate (3.3 g), industrial methylated spirit (15 ml) and water (2 ml) was heated under reflux for twenty hours. The cooled reaction mixture was poured into water and the oil which separated was cooled to give a solid which was recrystallised from industrial methylated spirit to give 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane oxime (m.p. 120—121°C).

A solution of the oxime prepared above (4.0 g) in ether (50 ml) was added slowly to a stirred suspension of lithium aluminium hydride (0.9 g) in ether (50 ml) under nitrogen. The mixture was heated under reflux for one hour and, after cooling, water and then a 20% aqueous solution of Rochelle's salt (potassium sodium tartrate tetrahydrate) (27 ml) and a 10% aqueous solution of sodium hydroxide (6 ml) added. The reaction mixture was stirred for one hour and then continuously extracted with ether during eighteen hours. The ether extract was dried and the ether removed to leave a solid from which 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine was separated by high pressure liquid chromatography. The product was identified by standard analytical techniques as the compound of Example 1 in the form of its free base.

Example 25

A 1M solution of diisobutylaliminohydride in hexane (200 ml) was added under nitrogen to a solution of 1-phenyl-1-cyclobutane carbonitrile (31.4 g) in ether (100 ml) at a temperature below −30°C. The temperature was maintained below 0°C for thirty minutes and 5N hydrochloric acid (200 ml) at a temperature of −10°C added. The reaction mixture was washed with petroleum ether (b.p. 60—80°C) and then warmed to 40°C. The reaction mixture was extracted with petroleum ether (b.p. 60—80°C) and the extract dried and evaporated to yield 1-phenyl-1-cyclobutane-carbaldehyde as an oil.

Methylamine was bubbled through a solution of the aldehyde (9.4 g) prepared as above in toluene (100 ml) whilst the temperature of the reaction mixture was maintained below 0°C. Magnesium sulphate (20 g) which had been dried over a flame and then cooled under nitrogen was added to the reaction mixture which was left for sixteen hours at room temperature before being filtered. The toluene was then removed by evaporation and the residue dissolved in ether (50 ml). This solution was added to a solution of propyllithium prepared by slowly adding excess propyl bromide (12.8 g) to a suspension of lithium (1.26 g) in ether (50 ml). The resulting mixture was left for sixteen hours at room temperature. A trace of unreacted lithium was removed by filtration and the filter washed with ether, water and then 5N hydrochloric acid. The filtrate and washings were heated on a steam bath for one hour. After cooling the reaction mixture was washed with ether and the aqueous layer was basified using aqueous sodium hydroxide solution. The reaction mixture was extracted with ether and the extract dried and the ether removed to give a residue from which *N*-methyl-1-(1-phenyl-cyclobutyl)butylamine (b.p. 80—86°/0.1 mm Hg.) was distilled.

The amine (2.3 g) prepared as described above was dissolved in ether (40 ml) and hydrogen chloride gas passed through the solution to precipitate *N*-methyl-1-(1-phenylcyclobutyl)butylamine

Exampl 26

A solution of 1-(3-chloro-5-methyl)-1-cyclobutanecarbonitrile (8.0 g) in ether (40 ml) was added to a solution of propyl magnesium bromide [prepared by the reaction of 1-bromopropane (6.7 g) and magnesium (1.3 g)] in ether (80 ml) and the mixture heated under reflux for two and a half hours. Two thirds of the ether was evaporated off and then, after cooling, a solution of sodium borohydride (3.5 g) in ethanol (150 ml) added. The mixture was maintained at 50°C for one hour and water (50 ml) and then 5N hydrochloric acid (50 ml) added. The ether layer was separated, dried and evaporated to yield a solid which was recrystallised from propan-2-ol to give 1-[1-(3-chloro-5-methyl)cyclobutyl]-butylamine hydrochloride (m.p. 145—146°C).

The hydrochloride salt prepared as above was shaken with ether and 5N sodium hydroxide solution and the ether layer evaporated to give the primary amine which was converted into *N,N*-dimethyl-1-[1-(3-chloro-5-methyl)cyclobutyl]butylamine hydrochloride (m.p. 148°C) (Formula I n=0; R_1=propyl; R_2=H; R_3 and R_4=Me; R_5=3-Cl and R_6=5-Me) in a similar manner to that described in Example 2.

Example 27

1-(4-Chlorophenyl)-1-cyclobutanecarbonitrile (37.6 g) prepared in a similar manner to the 1-(3,4-dichlorophenyl)-1-cyclobutanecarbonitrile described in Example 1 was added to a solution of potassium hydroxide (32.4 g) in diethyleneglycol (370 ml) and the mixture heated under reflux for three and a half hours. The reaction mixture was poured into an ice/water mixture and the resulting solution was washed with ether. The aqueous layer was added to a mixture of concentrated hydrochloric acid (100 ml) and ice and the resulting precipitate of 1-(4-chlorophenyl)-1-cyclobutanecarboxylic acid (m.p. 86°—88°C) collected, washed with water and dried.

A solution of the acid (10.5 g) prepared as above in tetrahydrofuran (150 ml) was added dropwise under nitrogen to a stirred suspension of lithium aluminium hydride (2 g) in tetrahydrofuran (150 ml). The mixture was stirred under reflux for two hours and water added. The mixture was filtered through diatomaceous earth (Celite-RTM) and the product extracted into ether. After washing with water and drying, the ether was evaporated to give a residue which was recrystallised from petroleum ether (b.p. 60—80°). The product was 1-[1-(4-chlorophenyl)cyclobutyl]methyl alcohol (m.p. 60—62°C).

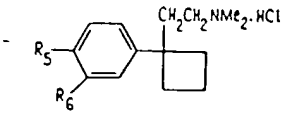
A solution of the alcohol prepared as described above (60 g) in pyridine (52 ml) was added dropwise to a solution of p-toluenesulphonylchloride (60 g) in pyridine (100 ml) cooled in ice. The temperature was allowed to rise to room temperature and remain there for eighteen hours. 1-[1-(4-Chlorophenyl)cyclobutyl]methyl p-toluene sulphonate (m.p. 99—100°C) was precipitated by pouring the reaction mixture into a mixture of ice and concentrated hydrochloric acid (200 ml).

A solution of the sulphonate compound (97 g) prepared as described above and sodium cyanide (16.6 g) in dimethyl sulphoxide (370 ml) was heated on a steam bath for eighteen hours. The mixture was poured into water and extracted with ether. After washing and drying the ether was evaporated to leave a solid residue of 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile (m.p. 63—65°C).

The acetonitrile prepared above (20 g) was dissolved in ether (120 ml) and the solution added dropwise under nitrogen to a stirred suspension of lithium aluminium hydride (5.84 g) in ether (80 ml). The mixture was stirred at ambient temperature for one and a half hours and then under reflux for a further two hours. Water was added dropwise and the resulting mixture filtered through diatomaceous earth. The residue was washed with ether. The filtrate was extracted with ether and the combined ether portions were washed with water and extracted with 5N hydrochloric acid. The acid solution was washed with ether and aqueous NaOH was added. The product was extracted into ether and the extract washed with water, dried and evaporated to give a residue which on distillation gave 2-[1-(4-chlorophenyl)cyclobutyl]ethylamine (b.p. 119—121°/1.5 mm Hg).

The ethylamine prepared as described above (6.9 g), 98% formic acid (6.6 ml), water (0.9 g) and 37 to 40% aqueous formaldehyde solution (9 ml) were heated on a steam bath for eighteen hours. The mixture was cooled and excess concentrated hydrochloric acid added. A yellow solid residue was obtained on evaporation to dryness. The solid was partitioned with dichloromethane and 5N sodium hydroxide solution and the aqueous layer extracted with a further portion of dichloromethane. The dichloromethane portions were combined, washed with water, dried and evaporated to yield a solid residue which was dissolved in propan-2-ol (15 ml) and concentrated hydrochloric acid was added to pH 2. The mixture was evaporated to dryness and the residue recrystallised from ethyl acetate to give colourless crystals of *N,N*-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 220—222°C) (Formula I n=1; R_1, R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6, R_7 and R_8=H).

In a similar manner to that described above the following compounds were made



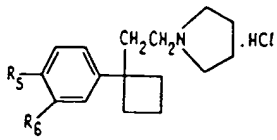
Example	R_5	R_6	m.p. of HCl salt
27(a)	Cl	Cl	218—220°
27(b)	I	H	263—265°
27(c)	—CH=CH—CH=CH—		234—236°

27(d) In a similar manner *N,N*-dimethyl-2-[1-(4-chloro-2-fluorophenyl)-cyclobutyl]ethylamine hydrochloride (m.p. 232—233°C (dec)) was prepared.

Example 28

2-[1-(4-Chlorophenyl)cyclobutyl]ethylamine (12 g) prepared as described in Example 27, 1,4-dibromobutane (12.4 g) and anhydrous sodium carbonate (14.3 g) were mixed in xylene (100 ml) and the mixture heated under reflux with stirring for sixteen hours. The mixture was cooled, filtered and the xylene removed by evaporation to give a residue which on distillation gave *N*-2-[1-(4-chlorophenyl)-cyclobutyl]ethylpyrrolidine (b.p. 148—150°/1.5 mm Hg) (Formula I n=1; R_1, R_2=H; R_3 and R_4 together with the nitrogen atom forming a pyrrolidine ring; R_5=4-Cl; R_6, R_7 and R_8=H).

In a similar manner to that described above the following compounds were made and isolated as their hydrochloride salts.



Example	R_5	R_6	m.p. of HCl salt
28(a)	Cl	Cl	213°
28(b)	—CH=CH—CH=CH—		232—233°

Example 29

A solution of 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile (30 g) prepared as described in Example 27 in ether (100 ml) was added to the reaction product of methyl bromide gas and magnesium turnings (5.95 g) in ether (80 ml). The mixture was heated under reflux for four hours. Ice and then concentrated hydrochloric acid (105 ml) were added and the mixture heated under reflux until all solid material had dissolved. The aqueous layer was washed with ether and the ether used for washing was combined with the ether phase of the reaction mixture. The combined ether extracts were washed with water, dried and evaporated to yield a residue which was distilled twice to yield 1-[1-(4-chlorophenyl)cyclobutyl]propan-2-one (b.p. 133—136°/2.5 mm Hg).

The ketone prepared as described above (5.4 g) was mixed with *N*-methylformamide (18 ml), 98% formic acid (4 ml) and 25% aqueous methylamine (0.6 ml) and the mixture heated under reflux for sixteen hours. The mixture was poured into water and extracted with dichloromethane. The extract was washed, dried and evaporated to give a residue which was heated under reflux with concentrated hydrochloric acid (10 ml) for six hours. The mixture was evaporated to dryness and the residue dried by repeated addition and vacuum evaporation of an industrial methylated spirit/toluene mixture. The solid residue was recrystallised from propan-2-ol to give *N*-methyl-2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 193—194°C) (Formula I n=1 R_1, R_2=H; R_3=Me; R_4=H; R_5=4-Cl; R_6=H; R_7=Me; R_8=H).

Example 30

A mixture of 1-[1-(4-chlorophenyl)cyclobutyl]propan-2-one prepared as described in Example 29 (15 g) and 98% formic acid (4 ml) was added dropwise to formamide (12 ml) at 160°C. The temperature was raised to 180°C and maintained at this temperature for ten hours. The mixture was cooled, diluted with water and extracted with dichloromethane. The extract was washed, dried and evaporated to yield a yellow oil which was hydrolysed with concentrated hydrochloric acid under reflux. The resulting aqueous solution after dilution with water was washed with ether, aqueous NaOH was added and the aqueous solution extracted with ether. The extracts were washed, dried and evaporated to yield a residue which on distillation gave 2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine (b.p. 105—107°/0.7 mmHg).

hydrochloric acid added dropwise until the pH was 2. Ether (110 ml) was added and colourless crystals of 2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 184—185°C) were collected. (Formula I n=1; R_1, R_2=H; R_3, R_4=H; R_5=4-Cl; R_6=H; R_7=Me and R_8=H).

Example 31

2-[1-(4-Chlorophenyl)cyclobutyl]-1-methylethylamine (3.94 g) prepared as described in Example 30, 1,4-dibromobutane (3.82 g), anhydrous sodium carbonate (4.4 g) and xylene (30 ml) were mixed and heated under reflux for sixteen hours. The mixture was cooled, filtered and evaporated to yield a residue which was distilled twice (b.p. 130—132°/0.5 mm Hg). The product of the distillation was dissolved in propan-2-ol (5 ml) and ether (70 ml) and concentrated hydrochloric acid added to pH 2. The solution was evaporated *in vacuo* and the residue recrystallised from ethyl acetate to give *N*-[2-[1-(4-chlorophenyl)cyclobutyl]-1-methyl]ethylpyrrolidine hydrochloride (m.p. 151—152°C) (Formula I n=1; R_1, R_2=H; R_3 and R_4 together with the nitrogen atom forming a pyrrolidine ring; R_5=4-Cl; R_6=H; R_7=Me; R_8=H).

Example 32

1-[1-(4-Chlorophenyl)cyclobutyl]propan-2-one prepared as described in Example 29 (25 g) and 98% formic acid (10 ml) were added to formamide (22 ml) at 160°C. The temperature was raised to 175°C and maintained at this temperature for sixteen hours. The mixture was cooled, extracted with dichloromethane. The extract was washed with water and evaporated to give a gum which was crystallised from petroluem ether (b.p. 40—60°C) to give *N*-formyl-2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine (m.p. 71—73°C).

N-formyl-2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine (11.06 g) prepared as described above was heated under reflux for six hours with a mixture of concentrated hydrochloric acid (34 ml), water (34 ml) and diethyleneglycoldimethyl ether (40 ml). The mixture was cooled, washed with ether and basified with aqueous sodium hydroxide. The basified solution was extracted into ether, washed with water, dried, evaporated and distilled to give 2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine (b.p. 119—121°C at 0.8 mm Hg). The amine (2.65 g) was dissolved in propan-2-ol (15 ml) and concentrated hydrochloric acid added to pH 2. Ether (110 ml) was added and crystals of 2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 184—185°C) were collected. (Formula I n=1; R_1, R_2=H; R_3, R_4=H; R_5=4-Cl; R_6=H; R_7=Me and R_8=H).

Example 33

2-[1-(4-Chlorophenyl)cyclobutyl]-1-methylethylamine (1.8 g) prepared as described in Example 32 was mixed with formic acid (4.5 ml). 37 to 40% Aqueous formaldehyde solution (6 ml) was added and the mixture heated first at 45—50°C for 30 minutes and then under reflux for two hours. The mixture was cooled, basified with aqueous sodium hydroxide, extracted with ether, the ether extract was washed with water and extracted with 5N hydrochloric acid. The acid extract was washed with ether, basified with aqueous sodium hydroxide, and extracted with ether. Hydrogen chloride gas was passed through the ether extract and a white solid was formed. The solid was collected and recrystallised from ethyl acetate to give *N,N*-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (m.p. 108—110°C) (Formula I n=1; R_1, R_2=H; R_3, R_4=Me; R_5=4-Cl; R_6=H; R_7=Me; R_8=H).

Example 34

A 70% solution of sodium bis(2-methoxyethoxy) aluminium hydride in toluene (sold under the trade mark Red-al) (35 ml) was added dropwise to a solution of *N*-formyl-2-[1-(4-chlorophenyl)-cyclobutyl]-1-methylethylamine prepared as described in Example 32 (5 g) in dry ether (110 ml) with cooling to maintain the temperature at less than 10°C. The temperature was allowed to rise to about 25°C and then the mixture was heated under reflux for two hours. The reaction mixture was poured into a mixture of crushed ice and concentrated hydrochloric acid. The resulting mixture was washed with ether, basified with aqueous sodium hydroxide and extracted with ether. The ether extract was washed with brine, dried and evaporated to give a liquid which was dissolved in petroluem ether (b.p. 40—60°C). Hydrogen chloride gas was bubbled through the solution to precipitate a solid which was recrystallised from propan-2-ol to give *N*-methyl-2-[1-(4-chlorophenyl)cyclobutyl]-1-methylethylamine hydrochloride (Formula I n=1; R_1, R_2=H; R_3=H; R_4=Me; R_5=4-Cl; R_6=H; R_7=Me and R_8=H) (m.p. 192—194°C).

Example 35

A solution in ether (80 ml) of 2-[1-(3,4-dichlorophenyl)cyclobutyl]acetonitrile (23 g) prepared in a similar manner to that described in Example 27 for 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile was added to the product of the reaction between magnesium turnings (3.53 g) and ethyl bromide (10.8 ml) in dry ether (80 ml) with stirring whilst heating on a steam bath. The ether was removed and replaced with toluene and the mixture heated under reflux for one hour. Water was added and the

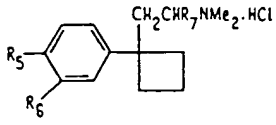
steam bath for one hour and filtered through a diatomaceous earth sold under the Registered Trade Mark Celite. The filtrate was extracted with dichloromethane and the extract washed with water and sodium bicarbonate solution and dried. The solvent was removed by evaporation and the residue distilled to give 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one (b.p. 149—150°/1.1 mm Hg).

The ketone prepared as above was converted into 1-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}-propylamine hydrochloride (m.p. 225—226°C) (Formula I n=1; R_1, R_2, R_3, R_4=H; R_5=4-Cl; R_6=3-Cl; R_7=Et; R_8=H) in a similar manner to that described in Example 32.

In a similar manner to that described above 2-[1-(3,4-dichlorophenyl)cyclobutyl]-1-methyl-ethylamine hydrochloride (m.p. 179°C) (Example 35a Formula I n=1; R_1, R_2, R_3 and R_4=H); R_5=4-Cl; R_6=3-Cl; R_7=Me and R_8=H) was prepared.

Example 36

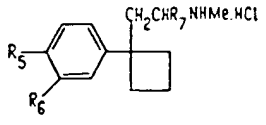
In a similar manner to that described in Example 33 compounds prepared in a similar manner to that described in Example 35 were converted into the corresponding *N,N*-dimethyl compounds.



Example	*Starting material*	R_5	R_6	R_7	*m.p.*
36(a)	35	Cl	Cl	Et	177—178°
36(b)	35(a)	Cl	Cl	Me	204—205°

Example 37

In a similar manner to that described in Example 34, *N*-formyl compounds prepared as described in Example 32 from ketones prepared as in Example 35 were converted into the corresponding *N*-methyl compounds.



Example	R_5	R_6	R_7	*m.p.*
37(a)	Cl	H	Et	170—172°
37(b)	Cl	Cl	Et	193—194°

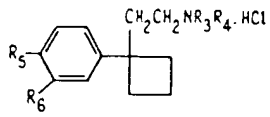
Example 38

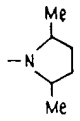
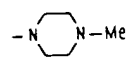
A mixture of 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile (10.1 g) prepared as described in Example 27, potassium hydroxide (8.1 g) and diethyleneglycol (92 ml) was heated under reflux for three and a half hours. The mixture was poured into an ice/water mixture and the resulting solution washed three times with ether and added to a mixture of ice and concentrated hydrochloric acid. On cooling a solid product separated which was recrystallised from petroleum ether (b.p. 62—68°C) with the use of charcoal. The recrystallised product was 2-[1-(4-chlorophenyl)cyclobutyl]acetic acid (m.p. 83—84°C).

The acid (5 g) prepared as described above was added to thionyl chloride (20 ml) and heated under reflux for one hour. Excess thionyl chloride was then removed and the residue poured into a solution of piperidine (3.8 g) in ether (20 ml). The mixture was stirred for thirty minutes and then water was added to dissolve piperidine hydrochloride. The ether layer was separated and the aqueous layer washed with ether. The combined ether portions were washed with water, dried and evaporated to yield a brown oil which was purified by distillation (b.p. 168°/1 mm Hg) and crystallisation from petroleum ether (b.p. 40—60°C). The solid product was *N*-2-[1-(4-chlorophenyl)cyclobutyl]-acetylpiperidine (m.p. 66—67°C).

A solution of the compound prepared as described above (2.7 g) in ether (20 ml) was added dropwise to a stirred mixture of lithium aluminium hydride (0.7 g) and ether under a nitrogen atmosphere. Stirring was continued for one hour at room temperature and then during heating under reflux for two hours. After cooling in ice, excess lithium aluminium hydride was decomposed by the addition of water. The mixture was filtered through diatomaceous earth (Celite). The aqueous portion of the filtrate was washed with a portion of ether and this portion was combined with ether portions which had been used to wash the solid residue. The combined ether portions were washed with water, dried and evaporated. The residue was purified by distillation. The product was *N*-2-[1-(4-

In a similar manner to that described above the following compounds were made and isolated as their hydrochloride salts by bubbling dry hydrogen chloride gas through a solution of the base in petroleum ether (b.p. 62—68°C).



Example	R_5	R_6	NR_3R_4	*m.p. (°C)*
38(a)	Cl	H		167—169°
38(b)	Cl	H		281—283° (dec)
38(c)	Cl	H		246—248°

Example 39

A mixture of sodium hydride (9 g), mineral oil (9 g) and dry dimethylformamide (150 ml) was stirred under nitrogen at 0°C. A solution of *p*-toluenesulphonylmethyl isocyanide which is sold under the trade name TosMIC (24.6 g) in dimethylformamide (50 ml) was added over twenty minutes. Absolute alcohol (18 g) was then added to the mixture at 0°C over a period of one hour. 1-Acetyl-1-(4-chlorophenyl)cyclobutane (24 g) prepared in a similar manner to that described in Example 1 for 1-acetyl-1-(3,4-dichlorophenyl)cyclobutane dissolved in dry dimethylformamide (20 ml) was added and the mixture was stirred for sixteen hours during which the temperature rose to ambient temperature. The mixture became viscous and petroleum ether (b.p. 80—100°C) (25 ml) was added. The mixture was poured into water and the pH adjusted to 6 by the addition of 5N hydrochloric acid. The resulting mixture was extracted with ether and the ether extract washed with water, dried and partially evaporated. A brown solid separated and was removed by filtration and the filtrate was evaporated and 2-[1-(4-chlorophenyl)cyclobutyl]propionitrile (b.p. 128—136°/0.6 mm) collected by distillation.

A solution of the propionitrile prepared as described above (3.5 g) in dry ether (20 ml) was added dropwise to a stirred mixture of lithium aluminium hydride (0.9 g) in dry ether (20 ml) at a temperature in the range 15 to 20°C. The mixture was stirred at ambient temperature for two hours and then during heating under reflux for a further three hours. 5N Sodium hydroxide solution (20 ml) and water (50 ml) were added and the mixture filtered through diatomaceous earth (Celite). The filter medium was washed with ether and the washings combined with the ether of the reaction mixture. The combined extracts were extracted with 5N hydrochloric acid. A solid formed at the interface which was collected by filtration, washed with acetone and dried. The solid was 2-[1-(4-chlorophenyl)cyclobutyl]-propylamine hydrochloride (m.p. 210—230°C).

The hydrochloride salt (1.0 g) prepared as above was dissolved in water, 5N aqueous sodium hydroxide solution was added and the solution extracted with ether. The ether extract was dried and evaporated to yield an oil which was heated under reflux for six hours with 1,4-dibromobutane (0.82 g), anhydrous sodium carbonate (0.96 g) and xylene (6.5 ml). The mixture was cooled, filtered through diatomaceous earth (Celite) and evaporated to dryness. The residue was dissolved in propan-2-ol (10 ml) and concentrated hydrochloric acid (5 ml) added. The mixture was evaporated to dryness and the residue collected, washed with ether and dried. The product was *N*-2-[1-(4-chlorophenyl)cyclobutyl]-propylpyrrolidine hydrochloride (m.p. 238—248°C) (Formula I n=1; R_1=Me; R_2=H; R_3 and R_4 together with the nitrogen to which they are attached forming a pyrrolidine ring; R_5=4-Cl; R_6, R_7 and R_8=H).

Example 40

A solution of 1-(3,4-dichlorophenyl)-1-cyclobutane carbonitrile (70 g) prepared in a similar manner to that described in Example 1 in industrial methylated spirit (200 ml) was mixed with a solution of sodium hydroxide (3.7 g) in water (5 ml) and 30% hydrogen peroxide solution added dropwise. The mixture was heated at 50°C for one hour and then stirred with 10% palladium on charcoal (0.5 g) for one hour. The mixture was filtered and evaporated to dryness to give 1-(3,4-dichlorophenyl)-1-cyclobutanecarboxamide.

The carboxamide prepared above was dissolved in dioxane (500 ml) and concentrated hydrochloric acid (100 ml) and then a solution of sodium nitrite (35 g) in water (80 ml) were added dropwise. The mixture was heated at 85 to 95°C for sixteen hours and then poured into water. The mixture was extracted with ether and the extract back-extracted with aqueous potassium carbonate. The basic extract was washed with ether and acidified with concentrated hydrochloric acid to give 1-(3,4-dichlorophenyl)-1-cyclobutanecarboxylic acid (m.p. 120—121°C).

The acid prepared as above was converted into the compound of Example 27(a) in a similar manner to that described in Example 27 and the compound of Example 28(a) in a similar manner to that described in Example 28.

Example 41

A solution of 2-[1-(3,4-dichlorophenyl)cyclobutyl]acetonitrile (23 g prepared in a similar manner to 2-[1-(4-chlorophenyl)cyclobutyl]acetonitrile described in Example 27) in dry ether (50 ml) was added to a solution of ethyl magnesium bromide prepared by the dropwise addition of ethyl bromide (15.83 g) in dry ether (80 ml) to a stirred mixture of magnesium turnings (3.53 g) and ether (80 ml). The mixture was heated under reflux for 30 minutes and stirred without further heating for 16 hours and then under reflux for a further two hours. 1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-butaniminyl magnesium bromide was collected by filtration and a sample of the solid (about 1 g) was added to a solution of sodium borohydride (3 g) in diethyleneglycoldimethyl ether (30 ml). The mixture was stirred at 45°C for 90 minutes. The reaction mixture was extracted with 5N hydrochloric acid. The aqueous phase was basified with aqueous sodium hydroxide solution and extracted with ether. The ether extract was dried and hydrogen chloride gas passed into the extract to precipitate 1-[[1-(3,4-dichlorophenyl)-cyclobutyl]methyl]propylamine hydrochloride (m.p. 223—224°C) (Formula I n=1; R_1, R_2, R_3 and R_4=H; R_5=4-Cl; R_6=3-Cl; R_7=Et; R_8=H).

Example 42

Formic acid (7 ml) was added dropwise to pyrrolidine (15 ml) at a temperature in the range 135—140°C. 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one (3 g) prepared as described in Example 35 was added dropwise and the mixture heated at 140°C for one hour. The temperature was raised to 185—190°C for sixteen hours. The reaction mixture was cooled and poured into 5N hydrochloric acid. The solution was washed with ether, basified and extracted with ether. The ether extract was dried and hydrogen chloride gas passed into the extract. Evaporation to dryness gave a solid which was triturated with dry ether and recrystallised from a mixture of petroleum ether and propan-2-ol to give *N*-1-[[1-(3,4-dichlorophenyl)cyclobutyl]methyl]propylpyrrolidine hydrochloride (m.p. 157—160°C) (Formula I n=1; R_1, R_2=H; R_3 and R_4 together with the nitrogen atom forming a pyrrolidine ring; R_5=4-Cl; R_6=3-Cl; R_7=Et and R_8=H).

Example 43

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-butaniminyl magnesium bromide (25 g) prepared as described in Example 41 was heated at 90—95°C for two hours with a mixture of concentrated hydrochloric acid (20 ml) and water (30 ml). The reaction mixture was extracted with ether and the ether extract dried and evaporated to dryness. 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one (b.p. 122—124° at 0.1 mm Hg) was distilled.

A mixture of 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one (4.3 g) prepared as described above, hydroxylamine sulphate (2.65 g), sodium acetate (4.0 g), industrial methylated spirit (56 ml) and water (23 ml) was stirred at ambient temperature for sixteen hours. The reaction mixture was extracted with ether. The ether extract was washed with water, dried and evaporated to give a solid which was recrystallised from petroleum ether (b.p. 80—100°C) to give 1-[1-(3,4-dichlorophenyl)-cyclobutyl]butan-2-one oxime (m.p. 106—110°C).

A solution of trifluoroacetic acid (2.33 ml) in tetrahydrofuran (5 ml) was added to a stirred suspension of sodium borohydride (1.13 g) in tetrahydrofuran (30 ml) over a period of five minutes. A solution of the oxime (1.7 g) prepared as described above in tetrahydrofuran (25 ml) was added dropwise and the mixture heated under reflux for six hours. The mixture was cooled and water (25 ml) and then 5N sodium hydroxide solution (25 ml) were added. The mixture was extracted with ether and the extract washed with water, dried and evaporated to give a residue which was dissolved in petroleum ether (25 ml). Dry hydrogen chloride gas was passed through the ether solution to give 1-[[1-(3,4-dichlorophenyl)cyclobutyl]methyl]propylamine hydrochloride (m.p. 222—224°C). (Formula I n=1; R_1, R_2, R_3 and R_4=H; R_5=4-Cl; R_6=3-Cl; R_7=Et and R_8=H).

Example 44

A solution of 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one (5.0 g) prepared as described in Example 43 and methoxy-amine hydrochloride (1.63 g) in a mixture of pyridine (60 ml) and ethanol (60 ml) was heated under reflux for 72 hours. The reaction mixture was evaporated to dryness and a mixture of water and ether added to the residue. The ether layer was washed with sodium bicarbonate solution and water, dried and evaporated to give 1-[1-(3,4-dichlorophenyl)cyclobutyl]butan-2-one oxime O-methyl ether.

The oxime ether prepared as described above (15 g) was then reduced to the product of Example 43 using sodium borohydride (0.95 g) in a similar manner to that described in Example 43.

cyclobutyl]butan-2-one (2.45 g) prepared as described in Example 42 and ammonium acetate (7 g) in methanol (28 ml) and the mixture stirred at room temperature for four days. Water (25 ml) was added dropwise with cooling. The aqueous mixture was extracted with ether and the ether layer washed with water and 5N hydrochloric acid (50 ml). The compound of Example 43 precipitated as a white solid.

Example 46

2-[1-(4-Chlorophenyl)cyclobutyl]acetic acid (1.5 g prepared as described in Example 38) was heated under reflux with thionyl chloride. Excess thionyl chloride was removed *in vacuo* and the residue added dropwise to a solution of cyclopropylamine (0.94 g) in ether (10 ml) and the mixture stirred for thirty minutes. Water was added and the aqueous phase extracted with ether. The ether extract was dried and the ether removed to give 2-[1-(4-chlorophenyl)cyclobutyl]-N-cyclopropylacetamide.

A solution of the amide prepared as above (1.45 g) in ether (15 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.42 g) in ether (7.5 ml) under nitrogen. The mixture was stirred at ambient temperature for one hour and then heated under reflux for a further two hours. After cooling, water (0.45 ml), then 15% sodium hydroxide solution (0.45 ml) and then water (1.35 ml) were added and the mixture stirred for fifteen minutes. The mixture was filtered and extracted with ether. The ether extract was shaken with N hydrochloric acid and a solid formed in the aqueous layer. The solid was *N*-cyclopropyl-2-[1-(4-chlorophenyl)cyclobutyl]ethylamine hydrochloride (m.p. 166—170°C).

A mixture of the hydrochloride salt (0.41 g) prepared as described above, sodium formate (0.1 g), 98% formic acid (1 ml) and 37—40% aqueous formaldehyde solution (0.5 ml) was heated at 85—90°C for eighteen hours. The reaction mixture was cooled and extracted with ether. The ether extract was washed with water, dried and filtered. Hydrogen chloride gas was passed through the filtrate which was then warmed to give a solid which was *N*-cyclopropyl-*N*-methyl-2-[1-(4-chlorophenyl)-cyclobutyl]ethylamine hydrochloride (m.p. 149—153°C). (Formula I n=1; R_1 and R_2=H; R_3=cyclopropyl; R_4=Me; R_5=4-Cl; R_6, R_7, and R_8=H).

Example 47

1-Acetyl-1-(3,4-dichlorophenyl)cyclobutane prepared as described in Example 1 (4.86 g) and cyclohexylamine (2.28 ml) were heated and stirred under reflux for 30 minutes. Stirring and heating was continued on an oil bath at 145°C for 3 hours. The product was cooled to ambient temperature, dissolved in methanol (50 ml) and sodium borohydride (0.8 g) added. The mixture was stirred at ambient temperature for twenty hours and then poured into water and the resulting mixture extracted with ether. The ether extract was washed with water and dried. After removal of the solvent N-cyclohexyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine (b.p. 144—156°/0.6 mm Hg) was obtained by distillation (Formula I R_1=Me; R_2=H; R_3=cyclohexyl; R_4=H; R_5=4-Cl; R_6=3-Cl).

Example 48

Pharmaceutical compositions containing any one of the compounds of formula I disclosed in Examples 1 to 47 are prepared in the following manner.

Example 48(a)

Tablets are prepared from the following ingredients:

	Parts by Weight
Active Ingredient	50.0
Lactose	78.5
Polyvinylpyrrolidone	5.0
Maize Starch	15.0
Magnesium Stearate	1.5

The active ingredient, the lactose and some of the starch are mixed and granulated with a solution of the polyvinylpyrrolidone in ethanol. The granulate is mixed with the stearic acid and the rest of the starch and the mixture is compressed in a tabletting machine to give tablets containing 50.0 mg. of the active ingredient.

Example 48(b)

Capsules are prepared in the following way. A mixture of the active ingredient (45 parts by weight) and lactose powder (205 parts by weight) is filled into hard gelatin capsules, each capsule containing 45 mg. of the active ingredient.

Example 48(c)

In the preparation of enteric coated tablets, the tablets described in Example 48(a) are given a thin coat of shellac varnish, followed by 20 coats of cellulose acetate phthalate in a manner well known in the art. In a similar manner the capsules of Example 48(b) may be provided with an enteric coating.

Exampl 48(d)

Vials containing a solution of water-soluble compounds of the present invention suitable for injection are prepared from the following ingredients:

Active Ingredient	1100 g.
Mannitol	1100 g.
Water, freshly distilled	to 11 litres

The active ingredient and mannitol are dissolved in some of the water and the volume of the solution is adjusted to 11 litres. The resulting solution is sterilised by filtration and filled into sterile vials each containing 1.65 ml. of solution.

Example 48(e)

In the preparation of suppositories, 100 parts by weight of the finely ground active ingredient is incorporated in 1214 parts by weight of triglyceride suppository base and the mixture is formed into suppositories each containing 100 mg. of the active ingredient.

In the preceding Examples novel ketones of formula V have been disclosed in which R_1, R_5 and R_6 have the meaning given in Examples 1, 1(a) to 1(e), 3, 4, 4(a) to 4(e), 6, 7, 7(a), to 7(d) 9, 9(a) to 9(n), 10, 10(a) to 10(z), 10(aa), 10(bb), 11(i), 11(k) and 11(l). These novel ketones of formula V are prepared by hydrolysis of novel imines of formula XVI in which Y=MgBr and R_1, R_5 and R_6 have the meaning given in the Examples specified above.

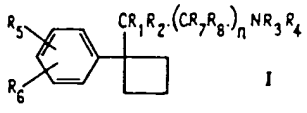
In the preceding Examples novel ketones of formula VI have been disclosed in which R_1, R_2, R_5, R_6 and R_7 have the meaning given in Examples 29, 35, 36 and 43. These novel ketones of formula VI were prepared by hydrolysis of novel imines of formula XVIII in which Y=MgBr and R_1, R_2, R_5, R_6 and R_7 have the meaning given in Examples 29, 35, 36 and 43.

In the preceding Examples novel cyano compounds of formula XVII are disclosed in which R_5 and R_6 have the meaning given in Examples 1, 1(d), 1(e), 4(g), 9(e), 9(m), 10(k), 10(e), 10(p), 10(r), 10(v), 10(y), 10(z), 10(aa), 10(bb), 11(k), 11(l) and 26.

In the preceding Examples novel formamides of formula XXVIII are disclosed in which R_1, R_3, R_5, R_6, R_7, R_8 and n have the meaning given in Examples 1, 1(a) to 1(e), 3, 4, 4(a) to 4(e), 6, 7, 7(a) to 7(d), 9, 9(a) to 9(n), 10, 10(a) to 10(z), 10(aa), 10(bb), 11(i), 11(k), 11(l), 29, 32, 35 and 36.

Claims

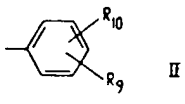
1. Compounds of formula I



I

in which n=0 or 1;

in which, when n=0, R_1 is a straight or branched chain alkyl group containing 1 to 6 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylalkyl group in which the cycloalkyl group contains 3 to 6 carbon atoms and the alkyl group contains 1 to 3 carbon atoms, an alkenyl group or an alkynyl group containing 2 to 6 carbon atoms or a group of formula II



II

in which R_9, and R_{10} which are the same or different, are H, halo or an alkoxy group containing 1 to 3 carbon atoms;

in which, when n=1, R_1 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_2 is H or an alkyl group containing 1 to 3 carbon atoms;

in which R_3 and R_4, which are the same or different, are H, a straight or branched chain alkyl group containing 1 to 4 carbon atoms, an alkenyl group having 3 to 6 carbon atoms, an alkynyl group having 3 to 6 carbon atoms, a cycloalkyl group in which the ring contains 3 to 7 carbon atoms, a group of formula $R_{11}CO$ where R_{11} is H or R_3 and R_4 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring having 5 or 6 atoms in the ring which optionally contains further hetero atoms in addition to the nitrogen atom;

in which R_5 and R_6, which are the same or different, are H, halo, trifluoromethyl, an alkyl group containing 1 to 3 carbon atoms, an alkoxy or alkylthio group containing 1 to 3 carbon atoms, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring

substituents of the second benzene ring together with the two carbon atoms to which they are attached form a further benzene ring;
and in which R_7 and R_8 which are the same or different are H or an alkyl group containing 1 to 3 carbon atoms;
and their pharmaceutically acceptable salts.

2. Compounds of formula I as claimed in claim 1 in which n=0, R_1 is a straight or branched chain alkyl group containing 1 to 4 carbon atoms, a cycloalkyl group containing 3 to 7 carbon atoms, a cycloalkylmethyl group in which the cycloalkyl ring contains 3 to 6 carbon atoms or a group of formula II in which R_9 and R_{10} are H, fluoro or methoxy and in which R_2 is H or methyl.

3. Compounds of formula I as claimed in claim 2 in which R_1 is methyl, ethyl, popyl, isopropyl, butyl, isobutyl, secondary butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl or phenyl.

4. Compounds of formula I as claimed in claim 1 in which n=1, R_1 is H or methyl and R_2 is H.

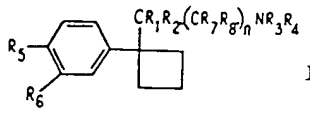
5. Compounds of formula I as claimed in any one of the preceding claims in which R_3 and R_4 are H, methyl, ethyl or formyl.

6. Compounds of formula I as claimed in any one of claims 1 to 4 in which R_3 and R_4 together with the nitrogen to which they are attached form a heterocyclic ring containing one nitrogen atom and 4 or 5 carbon atoms which is optionally substituted by one or more alkyl groups, or they form a heterocyclic ring containing a second nitrogen atom which is optionally alkylated or they form a heterocyclic ring containing one or more double bonds.

7. Compounds of formula I in which R_5 and R_6 are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by halo.

8. Compounds of formula I as claimed in any one of claims 1, 4, 5, 6, 7 or 8 in which R_7 is H, methyl or ethyl and R_8 is H.

9. Compounds as claimed in claim 1 of formula III

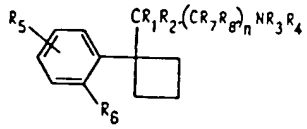


III

in which R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and n are as defined in claim 1.

10. Compounds as claimed in claim 9 in which R_5 and R_6, which are the same or different, are H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy, phenyl or R_5 and R_6 together with the carbon atoms to which they are attached form a second benzene ring optionally substituted by a chloro group.

11. Compounds as claimed in claim 1 of formula IV



IV

in which R_1, R_2, R_3, R_4, R_5, R_7, R_8 and n are as defined in claim 1 and R_6 is fluoro or methyl.

12. Compounds of formula IV as claimed in claim 11 in which R_5 is H, fluoro, chloro, bromo, iodo, trifluoromethyl, methyl, methoxy or phenyl and in which R_6 is fluoro or methyl.

13. Compounds of formula I named in Table I herein.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I claimed in any one of the preceding claims.

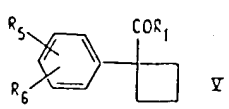
15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula III claimed in claim 9 or claim 10.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula IV claimed in claim 11 or claim 12.

17. A pharmaceutical composition as claimed in any one of claims 14, 15 or 16 in unit dosage form.

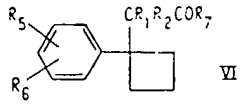
18. A pharmaceutical composition comprising a therapeutically active amount of a compound claimed in claim 13.

19. A process for the preparation of compounds of formula I comprising the reductive amination of ketones of formula V



V

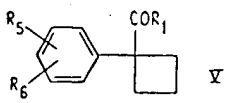
to give compounds in which n=0; R_2=H, R_4=CHO and R_1, R_5 and R_6 are as defined above or of ketones or aldehydes of formula VI



VI

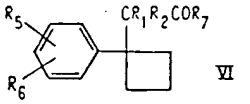
to give compounds in which n=1; R_4=CHO, R_8=H and R_1, R_2, R_5, R_6 and R_7 are as defined above.

20. A process for the preparation of compounds of formula I comprising reductive amination of ketones of formula V



V

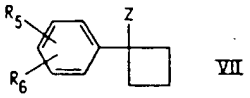
to give compounds in which n=0; R_2=H and R_1, R_5 and R_6 are as defined above or of ketones or aldehydes of formula VI



VI

to give compounds in which n=1; R_8=H and R_1, R_2, R_5, R_6 and R_7 are as defined above.

21. A process for the preparation of compounds of formula I comprising the reduction of compounds of formula VII



VII

in which

a) Z is a group of formula —CR=NOH or an ester or ether thereof to give compounds of formula I in which n=0 and R_2, R_3 and R_4 are H;

b) Z is a group of formula —CR_1=NR_3 to give compounds of formula I in which n=0 and R_2 and R_4 are H;

c) Z is a group of formula —CR_1=NY in which Y represents a metal-containing moiety derived from an organometallic reagent to give compounds of formula I in which n=0 and R_2, R_3 and R_4 are H;

d) Z is a group of formula —CR_1R_2CN to give compounds of formula I in which n=1 and R_3, R_4, R_7 and R_8 are H;

e) Z is a group of formula —$CR_1R_2CR_7$=NOH or an ester or ether thereof to give compounds of formula I in which n=1 and R_3, R_4 and R_8 are H;

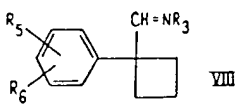
f) Z is a group of formula —$CR_1R_2CR_7$=NR_3 to give compounds of formula I in which n=1 and R_4 and R_8 are H;

g) Z is a group of formula —$CR_1R_2CR_7$=NY in which Y represents a metal-containing moiety derived from an organo-metallic reagent to give compounds of formula I in which n=1 and R_3, R_4 and R_8 are H;

h) Z is a group of formula —$CR_1R_2CONR_3R_4$ to give compounds of formula I in which n=1 and R_7 and R_8 are H.

22. A process as claimed in claim 21 in which Y is MgBr or Li.

23. A process for the preparation of compounds of formula I comprising (a) the reaction of an organometallic reagent with an imine of formula VIII

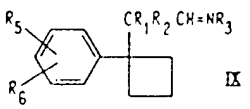


VIII

and (b) the hydrolysis of the resulting product to give compounds of formula I in which n=0.

24. A process as claimed in claim 23 in which the organometallic reagent is a Grignard reagent of formula R_1MgBr or an organolithium compound of formula R_1Li.

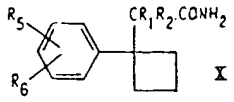
25. A process for the preparation of compounds of formula I comprising (a) the reaction of an organometallic reagent with an imine of formula IX



IX

26. A process as claimed in claim 25 in which the organometallic reagent is a Grignard reagent of formula R_7MgBr or an organolithium compound of formula R_7Li.

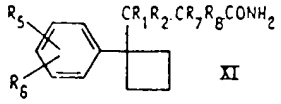
27. A process for the preparation of compounds of formula I comprising the decarboxylate rearrangement of (a) amides of formula X



X

to give amines in which n=0

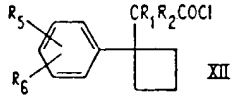
(b) amides of formula XI



XI

to give amines in which n=1

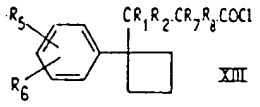
(c) acyl azides formed by reaction of sodium azide with acid chlorides of formula XII



XII

to give amines in which n=0

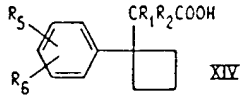
(d) acyl azides formed by reacting sodium azide with acid chlorides of formula XIII



XIII

to give amines in which n=1

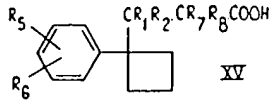
28. A process for the preparation of compounds of formula I comprising the reaction of hydrazoic acid with (a) carboxylic acids of formula XIV



XIV

to give amines in which n=0 or

(b) carboxylic acids of formula XV



XV

to give amines in which n=1

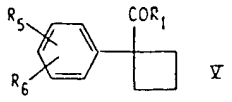
29. A process for the preparation of compounds of formula I in which R_4 is H comprising the hydrolysis of compounds of formula I in which R_4 is CHO.

30. A process for the preparation of compounds of formula I in which R_4 is methyl comprising the reduction of compounds of formula I in which R_4 is CHO.

31. A process for the preparation of compounds of formula I in which one or both of R_3 and R_4 is other than H comprising the conversion of a compound of formula I in which one or both of R_3 and R_4 are hydrogen to the required compound.

32. Compounds of formula I whenever made by a process claimed in any one of claims 19 to 31.

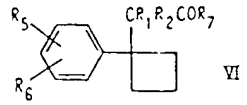
33. Compounds of Formula V



V

in which R_1, R_5 and R_6 are as defined above with the proviso that when R_1 is methyl or ethyl R_5 is other than H.

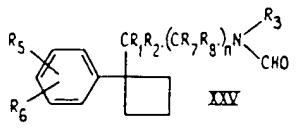
34. Compounds of formula VI



VI

in which R_1, R_2, R_5, R_6 and R_7 are as defined above.

35. Compounds of formula XXV



XXV

in which R_1, R_2, R_3, R_5, R_6, R_7, R_8 and n are as defined in claim 1.

36. Compounds of formula XVII disclosed herein as novel compounds.

37. Compounds of formula I described herein with reference to the Examples.

38. Compounds of formula III described herein with reference to the Examples.

39. Compounds of formula IV described herein with reference to the Examples.

40. Compounds of formula V described herein with reference to the Examples.

41. Compounds of formula VI described herein with reference to the Examples.

42. Compounds of formula XXV described herein with reference to the Examples.

43. Pharmaceutical compositions comprising a therapeutically active amount of a compound as claimed in any one of claims 37, 38 or 39.

44. A process for preparing compounds of formula I substantially as hereinbefore described with reference to the Examples.

45. 1-[1-(4-chlorophenyl)cyclobutyl]butylamine and its pharmaceutically acceptable salts.

46. *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]butylamine and its pharmaceutically acceptable salts.

47. *N*-methyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine and its pharmaceutically acceptable salts.

48. *N,N*-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]butylamine and its pharmaceutically acceptable salts.

49. *N*-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and its pharmaceutically acceptable salts.

50. *N,N*-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and its pharmaceutically acceptable salts.

51. *N,N*-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]-3-methylbutylamine and its pharmaceutically acceptable salts.

52. 1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine and its pharmaceutically acceptable salts.

53. *N,N*-dimethyl-1-[1-(3,4-dichlorophenyl)cyclobutyl]ethylamine and its pharmaceutically acceptable salts.

54. α-[1-(4-chlorophenyl)cyclobutyl]benzylamine and its pharmaceutically acceptable salts.

55. 1-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}propylamine and its pharmaceutically acceptable salts.

56. *N,N*-dimethyl-1-{[1-(3,4-dichlorophenyl)cyclobutyl]methyl}propylamine and its pharmaceutically acceptable salts.

57. *N,N*-dimethyl-2-[1-(4-iodophenyl)cyclobutyl]ethylamine and its pharmaceutically acceptable salts.

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ROHM PHARMA GMBH *EP --35-597
08.03.80-DE-008993 *(16.09.81)* A61k-31/13 C07c-87/45
Compsn. for treating Parkinson syndrome - contains optically active trans-2-phenyl cyclopropyl-amine

B(10-B4B, 12-C4) 2

27

D/S: E(AT CH DE FR GB IT LI).

Compsn. for treating Parkinson's syndrome contains as active ingredient (+)-trans-2-phenylcyclopropylamine (I) and/or its pharmaceutically acceptable acid addn. salt, practically free of the (-) optical enantiomer. Pref. unit doses contain 1-100, esp. 1-20, mg.(I).

DETAILS

(I) is prepd. from its racemate by standard techniques of resolution and formulated with conventional carriers and auxiliaries for enteral or parenteral (esp. oral) administration. The pref. daily dose is 1-10 mg./day. The use of (I) requires the same precautions as the use of monoamine oxidase inhibitors.

EXAMPLE

4.04g. (I) sulphate, 0.5g. Mg stearate and 95.46g. lactose (DAB) were blended in a mill, then the mixt. sieved through a 1.06 mm.-mesh screen, and filled into hard gelatin capsules (size no.4). Each capsule contains 6.87 mg.(I). (11pp1251).
(G) ISR: No-Citns.

EP--35597